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REFLECTIONS ON MALIGNANT LYMPHOMA

JANEWAY LECTURE, 1956*

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MAY I first express to the members of the Program Committee and to the Society a profound appreciation of having been highly honored by the invitation to give this lecture, named for Harry Harrington Janeway. Born eighty-three years ago, on March 19, 1873, he, among his other achievements, became a great pioneer in the therapeutic use of radium.

Doctor Janeway died February 1, 1921, only a little over five months after I first went to work at the old Memorial Hospital. I never saw him there, as he was then ill. I had seen him just once when I was a clinical clerk as a senior Cornell medical student at Bellevue Hospital, when he came one day to administer radium to a patient with intraoral cancer. My first position at Memorial Hospital as Clinical Assistant to the then Clinical Director, Doctor Stone, brought me into frequent association with such of the other pioneers as Ewing, Quick, Failla, Quimby, Lee, William B. Coley, Barringer, Bailey, and Healy.

The tremendous growth of the field of cancer as an investigational and therapeutic problem since those days can be traced back directly in large part to the efforts of such early workers as Janeway and these, his colleagues and successors.

No little part of the greatly expanded interest in cancer has pertained to leukemias and lymphomas, especially in the last fifteen years. Therefore, in casting about for a suitable topic for this lecture, it seemed timely to wander over the area of malignant lymphomas, and to reflect a little on some of their features, and on what is being done about these diseases.

What about the present status of treatment of malignant lymphomas? It seems all too obvious that, despite all the therapeutic agents that have been added in the past fifteen years, we still need something far better than what we have today. The radioactive isotopes, nitrogen mustards, triethylenemelamine, and similar chemical agents, and the various hormonal agents have significantly contributed only to palliation. While the future of chemotherapy of cancer is spoken of in glowing terms of hope, it must be admitted that it is chiefly in treatment of lymphomas and leukemias that the best results of chemo-

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therapy are seen. And yet in this, the best field, the results are, on the whole, disappointing.

Can one, indeed, expect to find chemical agents that can wipe out all traces of a lymphomatous process—to say nothing of other forms of cancer less responsive to currently available agents—without at the same time irreparably damaging normal cells? To me, the problem seems fundamentally different from that of bacterial infections and their treatment by antibiotics. The microbe is like an enemy alien in a country able to muster more or less effective counter-measures against him. The cancer cell or lymphoma cell is like a citizen secretly perverted to sabotage and thus readily able to infiltrate peaceful organizations and against whom defenses are, if any, at the best weak.

RADIOTHERAPEUTIC ISOTOPES

Of the radioactive isotopes, P^{32} is the one that has been the most extensively used in the lymphoma-leukemia field. While the differential absorption ratio of P^{32} gave some promise of sufficiently selective pick-up to merit its trial in malignant lymphomas, the actual palliative results were disappointing as compared with those in chronic leukemias and polycythemia vera. As an exception, I recall one case of lymphosarcoma presenting multiple cutaneous nodules of the disease, demonstrated to be very radiosensitive to local roentgen therapy. That case promptly showed rather striking, but yet only partial, regression of many of the skin lesions following the use of P^{32}. Re-analysis of our results in lymphosarcoma fails to show any over-all value of P^{32} in the treatment of that disease. It took no more than a few trials in Hodgkin's disease to show that P^{32} was likely to do more harm than good in that condition; similarly, in plasma cell myeloma. In a case of late and far advanced mycosis fungoides, although the differential absorption ratio of P^{32} was about 23 to 1 in some of the many cutaneous tumors, and therefore one might have expected a striking regression of at least some of the lesions, no regression whatsoever took place following a full therapeutic dose of P^{32}.

There has been pretty general agreement concerning the unsatisfactoriness of P^{32} for malignant lymphomas. In consequence, the use of P^{32} in the lymphoma-leukemia field is practically restricted to palliative treatment of chronic leukemias and polycythemia vera. Even in these latter fields of application, to digress a moment from the discussion of malignant lymphomas, P^{32} is far from a completely satisfactory therapeutic agent. In the chronic leukemias its chief effect appears to be as a depressant of the marrow and an agent destroying the excessive number of white blood cells. It cannot be expected, as a rule, to reduce markedly any bulky deposit of leukemic disease such as a greatly enlarged spleen or masses of greatly enlarged lymph nodes. In polycythemia vera, it may in some cases, some weeks following its administration, produce a marked lowering of hemoglobin, hematocrit and red blood cell count, and symptomatic betterment, but in other cases very little result may follow its use.

Although P^{32} is currently considered by many as the treatment of choice for polycythemia vera, I think we should never lose sight of the fact that in giving it we are putting into a patient a radioactive material, active all over the body and continuing to be active, with its exponential rate of decay, for a long time despite the relatively brief half-life of two weeks. We should think twice before committing this iatric insult, especially to an individual who may have a relatively stable type of polycythemia, with perhaps a prognosis of several to many years of life. This consideration appears, however, to be a theoretical one. A few years ago there was expressed in some circles a fear of inducing a conversion to leukemia in cases of polycythemia vera treated by P^{32}. Statements have been made in the literature to the effect that no case of polycythemia undergoes a conversion to leukemia unless

subjected to some type of radiation. While it is probably true that in the past two or three decades most cases of polycythemia have been treated at some time in their course with some type of radiation, I am nevertheless inclined to agree with those who look upon polycythemia as the erythropoietic analogue of leukemia, and to believe that a certain proportion of them will undergo change to leukemia, no matter what the method of treatment.

Were such a study possible, it would be of interest to compare cases of polycythemia treated solely by one of various methods, including phlebotomy, acetylphenylhydrazine, external irradiation and P^{32}. It seems unlikely that such a study would be possible, on presently available cases, because cases are relatively few and scattered, and most cases have been subjected to more than one method of treatment. In the experience at Memorial Center, we have not witnessed an increase in conversion to leukemia among our cases of polycythemia treated with P^{32}. Furthermore, aside from the withdrawal of blood, P^{32} does seem to be our best present resource for treatment of polycythemia vera.

CHEMOTHERAPEUTIC AGENTS

Our experience with nitrogen mustard began in 1944, while it was still a military secret. After testing various nitrogen mustard compounds, it appeared that the bis-betachloroethylamine hydrochloride compound known as HN_2 and now marketed as Mustargen was the most satisfactory one. While it has become practically indispensable because of its great usefulness in providing a rapid over-all effect, yet it, too, leaves much to be desired. Nitrogen mustard may be temporarily life-saving. By its so-called decongestant effect it may be most valuable in the initial treatment of the superior caval syndrome caused by massive mediastinal lymphoma, apparently obviating the risk of asphyxial reactions to the initial doses of roentgen therapy. Likewise, its decongestant effect may be important in the initial treatment of paraplegia caused by lymphomatous invasion of the spinal canal. Detoxification of the toxic patient with generalized febrile Hodgkin's disease may be brought about rapidly by nitrogen mustard.

In recent years we have often given the entire dose of 0.4 milligram per kilogram of body weight in a single injection. Provided the while blood cell count and platelets are at a reasonably good level, so that we feel it is safe to give the full dose of nitrogen mustard, we have preferred thus to reduce to one time the nausea and vomiting that usually follow the injection. To obtain quickly the maximum effect of nitrogen mustard is considered particularly desirable in such conditions as impending paraplegia or the superior caval syndrome, conditions which are regarded as emergencies.

When a patient with a known malignant lymphoma comes in with a paraplegia of very recent origin, say within a week, or when such a patient presents himself with such symptoms as paresthesias and beginning loss of motor function in the lower extremities, he is regarded as having an emergency condition. We prefer to localize the level of cord involvement as accurately as possible by neurologic examination and to proceed at once with treatment. We prefer to avoid any delay or risk of further damage to the cord that conceivably might be caused by such further examinations as lumbar puncture or myelography. We do not recommend laminectomy in such cases. Rather, having determined the affected level of the cord and taking into account that the actual spread of the lymphoma may well be for some distance both above and below the detectable level, appropriate radiation therapy is planned and now usually immediately preceded by a full dose of nitrogen mustard in one injection.

The purpose of preceding the radiation therapy by nitrogen mustard is to take advantage of the so-called decongestant effect of HN_2, so as to render less likely a congestant effect of the initial doses of roentgen therapy.

We began to use HN_2 preceding roentgen therapy in cases of paraplegia because it had been noted in the treatment of large mediastinal lymphomas that if HN_2 were given first one could safely begin at once with full fractional doses of roentgen therapy. So far as I am aware, there has occurred in our experience no asphyxial reaction to the initial dose of roentgen therapy such as was occasionally witnessed before this plan was used.

Before the days of nitrogen mustard and at present when treating any large mediastinal lymphoma if, for any reason, it is decided not to use mustard first, the initial dose of roentgen therapy to the mediastinal mass is small, in the order of 100 r in air or less, in order to minimize any possible asphyxial reaction due to the early congestant effect of radiation. In some cases after one or two treatments the patient is allowed to wait a day or two before proceeding with further treatment so as to let the reaction subside somewhat.

Seldom is our full course of HN_2 divided into more than two doses of 0.2 milligram each per kilogram of body weight. This is done only, as a rule, in those cases in which for some reason there is fear of giving the full dose of 0.4 milligram per kilogram in a single injection. The old method of divided doses of 0.1 milligram per kilogram daily for four days, still practiced by some, is not used at all. The main reason is that the patient is not much more upset by the dose of 0.2 or 0.4 milligram per kilogram than he would be by 0.1 milligram per kilogram and is only upset once or twice instead of four times. I have no evidence that giving the entire dose in one or at the most two injections is more effective or, on the other hand, that it is less effective than if divided according to the original method, but sometimes I wonder whether in some cases a greater division of dosage might not be more effective, in cases not requiring emergency relief.

Occasionally, in very ill patients, particularly those who have a somewhat precarious hematologic state, we give 0.1 milligram per kilogram and repeat according to indications a few times at intervals of five to seven days.

Yet how often does one see cases in which a full therapeutic dose of nitrogen mustard has caused chiefly leukopenia and thrombocytopenia without producing a significant betterment in the patient's lesions? In cases of reticulum cell sarcoma and Hodgkin's sarcoma, while there may be some brief regression, in many instances reactivation of the disease occurs all too soon, and unfortunately in some instances in a patient whose hematopoietic system has become too depressed by the course of nitrogen mustard just recently given to permit repeating it. We have learned to be particularly cautious in the administration of nitrogen mustard to cases of lymphocytic lymphosarcoma, as well as chronic lymphocytic leukemia, since they may be markedly sensitive to this agent.

There is no evidence that nitrogen mustard could produce the long remissions of malignant lymphoma that are occasionally produced by radiation. By long remissions I mean the control of the disease for fifteen to twenty years or more.

Triethylenemelamine, TEM, when available as a potent, undeteriorated product, acts essentially like nitrogen mustard. When used intravenously, it usually causes less vomiting, but what nausea or vomiting it does cause may in some cases last longer than the more severe nausea and vomiting caused by nitrogen mustard. When the available TEM for oral use is fresh and potent, it is a useful agent for those cases of generalized lymphoma not requiring the rapid action of intravenously administered nitrogen mustard, and in many cases rather remarkable maintenance may be achieved by protracted administration of small doses in the order of from 2.5 to 5 milligrams at intervals of from one to two weeks. Frequent checks of the blood cell count are necessary, particularly of the platelets, as well as of the white blood cells and hemoglobin. Our initial dose in Hodgkin's disease has become pretty much a routine of 2.5

milligrams daily for four days. It is important to have the patient take the TEM on a fasting stomach and abstain from food for at least one hour. This course of TEM is followed by re-examination and a blood cell count in two weeks. We have found no advantage in the use of such analogues as TEPA and Thiotepa, as compared with TEM.

Considering the over-all and ultimate effects of such chemotherapeutic agents as nitrogen mustard, TEM, and their analogues, although disliking a comparison of chemotherapy of cancer with the action of antibiotics, there is one aspect of the chemotherapy of malignant lymphomas about which one may speculate in analogy with bacterial resistance to antibiotics. The problem of the appearance of resistant strains of microorganisms is a harassing one that has assumed an increasing and sinister importance. The same phenomenon has been seen with insecticides. Now, while nitrogen mustard and the like no doubt have valuable palliative and indeed temporarily life-saving properties in some cases, they are general cell poisons. The dose that can safely be administered falls far short of a dose sufficient to sterilize all the malignant cells. Therefore, these agents must act because of their effect upon the tumor only to a limited degree, destroying or impairing the vitality of only the more sensitive cells and inevitably leaving behind to reproduce those cells of the tumor that are more resistant. It has seemed in practice that while we often more or less satisfactorily palliate the symptoms of the moment, nevertheless the relapses come all too soon and in some cases at least, in a more aggressive form. I cannot at present document the impression that thus, by a sort of Darwinian selection, favorable to the more aggressive and resistant lymphoma cells, but unfavorable to their unfortunate host, the patient, we have in these instances, so to speak, partly sacrificed the future for the sake of the present.

That principle of sacrificing the future for the sake of the present is one that sometimes has to be applied. For example, when one is faced with growing malignant lymphoma in a lung already the site of radiation fibrosis, when it appears that only further radiation offers a chance for palliation, one may feel forced to use radiation again, although the long-term prospect is for the production of further morbidity in the form of further pulmonary fibrosis. Yet how difficult it is to tell how much of the change visualized in the lung is radiation fibrosis and how much is persistent malignant lymphoma. In some cases of Hodgkin's disease in which we felt pretty much convinced that radiation fibrosis accounted for the lesions seen, postmortem examination showed that the shadows were caused by Hodgkin's fibrosis.

HORMONES

Hormonal therapy with ACTH, cortisone, or prednisone may be of considerable adjunctive value, but with few exceptions has not shown any striking worth in producing real regression of malignant lymphoma. Exceptions do occur, and partial regression may be seen following the use of these agents in Hodgkin's disease, in lymphosarcoma, particularly of the follicular type, and even in reticulum cell sarcoma and mycosis fungoides. Such results are far from consistent. The chief value of these agents is in symptomatic relief of itching, fever, and pain, to some extent in combating anemia, and particularly acquired hemolytic anemia, seen most commonly in chronic lymphocytic leukemia, less often in lymphosarcoma and other diseases in this field. There appears to be some indication that for acquired hemolytic anemia ACTH may be more effective than cortisone. Severe iatrogenic complications may be caused by these agents, so that there is increased awareness of the need for careful survey of the patient as a whole before subjecting him to the risks of such complications. The lighting up of a latent tuberculosis, the appearance of pneumonia, or of multiple lung abscesses,

exsanguinating hemorrhage from the gastrointestinal tract, or perforation of the gastrointestinal wall, to say nothing of diabetes, other metabolic disturbances, and mental aberrations, are unpleasant complications to have to deal with in patients already severely ill with a malignant lymphoma.

PLAN OF TREATMENT

The basis for our approach to a plan for treatment of malignant lymphomas is the relatively simple concept that we hope that the case that seems to have the disease limited to one site may actually have only that unicentric form of the disease, and that therefore aggressive treatment of that focus is justifiable in an attempt to cure. Thus, like many others, we attempt, when the patient is first seen, to classify the case as Class I, Class II, or Class III. Class I, apparently unicentric—the disease in only one site, without constitutional symptoms, or any abnormality of the blood cell count to suggest systemic spread. Class II, beginning spread but relatively regionally confined, with or without constitutional symptoms. A classic example is the patient with Hodgkin's disease or lymphosarcoma with mediastinal and supraclavicular lymph node enlargement who may, or may not, have a little fever or sweating at night. Class III is the case with generalization, more or less pronounced, and usually with constitutional symptoms.

This classification serves as a working basis on which to decide the method of treatment. The plan, of course, is to treat the unicentric focus aggressively, the regionally confined disease moderately heavily, and the generalized disease conservatively.

It seems a defeatist policy not to treat the apparently unicentric case by an aggressive local attack. If the malignant lymphoma is actually limited to one region, then sterilization of the disease in that region should cure the patient. Every now and then cases turn up which have had long survival, say ten years or more, without evidence of recurrence anywhere following treatment of the one region to which the disease seemed to be limited. Yet, we do not dare to call them cured, because other cases are seen in which, after a similarly long time, recurrence has appeared either in the same site, or more often in some other site and perhaps in a distant site. Does this mean anything like a metastasis from the original site, a metastatic-like spread that by some peculiar mechanism of partial immunity has been quiescent all these years? Or, does it mean a susceptibility of the cells of this patient to develop the same disease *de novo* in another site? When, for example, a patient whose mediastinal Hodgkin's disease has regressed some years ago and who has shown no other evidence of the disease since then is suddenly found to have a cluster of enlarged lymph nodes in the groin, the question is, "How did the disease get there?" Does it represent a spread by means of cells transported or having migrated from the original site, or does it mean the disease has arisen *de novo* in the groin lymph nodes because of attack by a virus or some as yet unknown etiologic agent?

This is not, I think, useless and idle speculation. It has a bearing upon our philosophy regarding therapy. If we knew the answer to this question about the mode of spread of malignant lymphoma, we would be in a better position to decide, for example, whether radiation therapy should be restricted to the region known to be affected, or whether we should practice what some have advocated, that is, treatment of contiguous node-bearing regions or even all the main node-bearing regions of the body.

Many of you will recall that some have practiced routine irradiation of large body sections, including the whole torso. We have never routinely practiced this method at Memorial Hospital, but rather have treated only those regions which were known to be or were strongly suspected of being involved. The reason has been the wish to avoid depleting the patient's reserves and a doubt that a patient could

tolerate doses all over his torso sufficient to prevent the development of lesions in some part distant from the original site.

The patient whose mediastinal Hodgkin's disease has regressed may have his next evidence of the disease in lung, abdomen, spleen, groin, spinal canal, or a pelvic bone. If he has been depleted by sectional irradiation of his entire torso, he will not be in good condition to withstand sufficient dosage to the newly affected site.

We used to do a fair amount of total body irradiation by the low-intensity Heublein method (0.86 to 1.6 r per hour), and still have the Heublein unit available for use. The advent of first P^{32} and then of chemotherapy has caused almost complete disuse of the Heublein method. Although it seemed valuable in some cases, it was quite unpredictable in its results, and necessitated admission of the patient for from one to three weeks, depending on the dose.

Our philosophy of the treatment of malignant lymphomas comprises aggressive treatment of the case that seems unicentric, and fairly aggressive treatment of the Class II case with beginning spread of the disease, but still showing regional distribution of lesions. This policy is followed in hopes of long control. We regard the Class III case with marked generalization as more like a case of leukemia and thus best treated cautiously. The objective is to do whatever may best keep the patient in comfort for the longest possible time.

It seems obvious that to treat a patient who has many and widely distributed external and internal lesions with heavy doses of radiation to all the lesions may only deplete him severely, and make him uncomfortable, and run a great risk, not only of failing to lengthen his life in comfort, but of shortening his life with discomfort.

In deciding what to do about the individual patient who presents a problem of previously untreated generalized malignant lymphoma, there cannot be any hard and fast rule for guidance. Each case calls for individualization, and judgment is empiric, influenced by various factors. A careful history, to give a background concept of the rapidity of development of this particular patient's lymphoma, is one of the most important factors in deciding about the treatment. Another consideration is: What is the probable present histology of the lesions in the more vital regions? That is to say, for example, if this patient two or three years ago had a biopsy of a peripheral lymph node showing giant follicular hyperplasia or follicular lymphosarcoma, but now he has a bulky mass of hard, centrally-located abdominal lymph nodes in the periaortic and mesenteric regions, and he has abdominal cramps and other symptoms suggesting partial intestinal obstruction or, if he has an osteolytic process with pain in the fourth or fifth lumbar vertebra, it may very well be that in those regions he has developed a more aggressive and radioresistant type of tumor which, histologically, would be called reticulum cell sarcoma.

To take another example, a patient who gives a history of Grade I general lymph node enlargement for two or three years had an earlier biopsy of a peripheral lymph node showing lymphocytic lymphosarcoma, but recently his spleen has become much larger, his skin shows a few pinkish, button-like plaques of infiltration, and, in addition to a moderate anemia, his white blood cell count has risen to 20,000, and the differential count for the first time shows 10 to 15 per cent unclassified cells. Is the application of aggressive roentgen therapy to all his enlarged lymph nodes and enlarged spleen going to do this patient any good? Probably not, since in all likelihood he will soon have a picture of acute stem-cell leukemia.

In contrast to the last case, along comes a man, aged fifty-five, with prominent enlarged rubbery lymph nodes in all of the main peripheral node-bearing regions, a firm spleen four finger-breadths down, but with a normal appearing mediastinum. He has not noticed any symptoms and has

continued to work daily without undue fatigue. A recent biopsy of a lymph node showed reticulum cell sarcoma. Will he be benefited by aggressive treatment with nitrogen mustard and roentgen therapy to all his detectable disease, or will he be better off with reassurance and observation until such time as he develops symptoms?

The question is often asked, "What do we advise regarding surgical removal of enlarged lymph nodes, particularly in the neck, when biopsy has shown Hodgkin's disease or some type of lymphosarcoma, including reticulum cell sarcoma, and the disease is apparently limited to one side of the neck?" The question of whether or not to do a radical surgical removal of unilateral neck lymph node malignant lymphoma is not answerable by a simple yes or no, in my opinion. Here, again, each case needs individualization. Nor do I believe, considering the difficulty of assembling cases just alike, that the question would be easily answered by assigning arbitrarily alternate cases to surgery. I believe that very rigid criteria would need to be applied in selection of those cases to which the alternate assignment would be applied.

At the present time, I believe there has not yet been sufficient correlated experience in radical removal of cervical lymph node malignant lymphoma to afford more than a suggestion of the value or lack of value of that procedure, and I do most definitely regard it as still an experiment. I see no great objection to the surgical removal of a bulky mass of lymph nodes when it is feasible to do so, and when the objective is simply to get rid of them quickly so as not to have to subject the patient to the undesirable effects of obliterative radiation therapy. Surgery can at times play a useful role in such a situation, but if one is thinking of radical surgery as an attempt to cure, I believe certain rigid criteria must be applied in any attempt to evaluate the procedure.

In our own too-limited experience, I fail to see demonstrated any value as far as cure or great prolongation of freedom from evidence of disease is concerned. Two years ago I examined the records of 10 cases in which a radical unilateral neck dissection had been done for apparently unicentric Hodgkin's disease. Nine of the 10 patients were males. The ages were far from comparable, varying from nine to eighty-four years. The extent of the disease varied widely. The eighty-four year old man had a lesion 3 centimeters in diameter in one cheek, and a submandibular lymph node 5 centimeters in diameter on the same side; while a twenty-three year old man had widespread enlargement of the lymph nodes on one side of the neck, extending from mastoid to clavicle and with slight displacement of the trachea to the opposite side, suggesting presence of enlarged lymph nodes in the thoracic inlet, and therefore probably in the upper mediastinum.

At the time of this review, 4 of the 10 patients were dead, having lived only from one to two years postoperatively. The 6 who survived had lived from two to six years postoperatively. Only 1 was free of evidence of disease, having then lived about four and one-half years following the operation. While none of the 10 had a recurrence at the site of radical neck dissection, and this fact perhaps speaks for the value of surgical extirpation versus obliterative roentgen therapy, nevertheless every case but 1 had developed activity of the disease elsewhere. The detection of disease activity elsewhere took place in from only one and one-half months to twenty-one months postoperatively. These results impressed me as rather discouraging for radical neck dissection from the point of view of seeking a curative method.

What do these results mean? I think these cases were too diversified to permit drawing any conclusions, but certain speculations may be indulged in.

First, does early appearance of activity of the disease elsewhere in these cases mean that the disease was arising multicentrically rather than unicentrically? No proof is available, and from clinical behavior as observed in other cases I think the evidence

tends the other way. I prefer to believe that at the time of operation undetected disease already existed in other regions. Such a reason for failure in the surgery of cancer in general is common and indicates the inadequacies of our methods of detection of the spread of cancer, rather than the impropriety of the surgical attack on what seems to be unicentrically confined cancer.

Second, is it advisable to do unilateral neck dissection for Hodgkin's disease when lymph nodes are found involved at the base of the neck? We think now it is so likely that in such cases there is also disease within the thorax or abdomen that the only value of surgery would be merely the quick removal of the known involved lymph nodes. Therefore, we now advise restricting selection for radical surgery of the neck to those cases with limitation of the detectable disease to the upper half of the neck.

Third, after radical surgery is done, should the operative field be given radiation therapy? We advise it in every case. Considering the cellular infiltrative character of malignant lymphoma, it is difficult at least for a non-surgeon to visualize how any surgeon can dissect out all the disease completely without skimming very close to it and perhaps leaving traces of it behind in some places. Therefore, we advocate giving as soon as possible as much radiation as the postoperative site can safely take, in hopes of sterilizing any residual disease.

Considering now the other types of malignant lymphoma, I would apply the same rules to reticulum cell sarcoma as to Hodgkin's disease with, perhaps, a little more misgiving in regard to a hidden primary lesion being present in the nasopharynx. But, if the selection of cases is limited to those with lymph nodes involved only in the upper half of the neck, and if postoperative radiation is given, one may feel that an undetected primary lesion in the nasopharynx is probably going to receive at least some radiation from the neck fields.

In the case of follicular lymphosarcoma and lymphocytic lymphosarcoma, I have somewhat more misgivings about the true unicentricity of what appears to be unicentric disease. These processes, more nearly allied to lymphocytic leukemia, may more commonly show beginning generalization when first detected, and have characteristically more of a tendency to present symmetric generalized lymphadenopathy and hepatosplenomegaly. Moreover, not infrequently there may develop a leukemic blood picture of the lymphocytic type, so that in finding an early apparently unicentric case of follicular or lymphocytic lymphosarcoma, one is more inclined to expect to see evidences of the disease in other than the originally detected site earlier than with Hodgkin's disease or reticulum cell sarcoma. Whether this means a greater likelihood of multicentric rather than unicentric origin in these types I cannot say. Exceptions do occur, and occasionally one may see long freedom from clinical evidence of disease elsewhere after adequate treatment of the orginally detected focus. Because of this seemingly greater tendency to early generalization, radical surgery of an initially detected single focus seems less suitable for follicular and lymphocytic lymphosarcoma than for Hodgkin's disease or clear-cut reticulum cell sarcoma.

One interesting aspect of malignant lymphomas is the way they may mimic other diseases. There are two examples which I would like to mention particularly.

Imitation of thyroid disease may be produced by Hodgkin's disease or any variety of lymphosarcoma. We find numerous examples of these malignant lymphomas growing in the neck in such fashion as to have been mistaken for goiters. The lymphoma may grow about, close to, or actually into the thyroid gland. Given such a setting, the condition may be thought to be a nodular goiter or even a carcinoma of the thyroid. It may be impossible to know whether one is dealing with thyroid cancer, with metastases to neck lymph nodes, or Hodgkin's disease involving the thyroid

region, or the thyroid itself, until the biopsy is seen. A patient with a malignant lymphoma may have symptoms and signs highly suggestive of hyperthyroidism. Also, the lymphoma patient may actually have true thyroid disease, be it hyperthyroidism, nodular goiter or carcinoma of the thyroid.

Another simulation by lymphoma in the mediastinum may cause a mistaken diagnosis of enlargement of the pulmonary conus. I recall, for example, the case of a college student who was watched from his freshman to his senior year, under the impression that he had some peculiar cardiac anomaly, and that a solitary enlarged lymph node in his groin was caused by epidermophytosis, until his lack of energy in his senior year caused restudy, showing marked enlargement of the mediastinum, and then biopsy of the inguinal lymph node showed Hodgkin's disease.

Time forbids further speculation or reflections about this, that, or the other feature of malignant lymphomas and their treatment.

While we should preach and practice a hopeful, forward-looking, aggressive attitude toward their treatment, we must at present acknowledge that we remain far from complacent about what we can do for these diseases today. Therefore, we must devoutly hope that present or future workers in this field may succeed in finding far better answers to their complex problems.

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A HISTORY OF ROENTGEN THERAPY

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IN ATTEMPTING to evaluate the importance of scientific contributions to medicine, it is often helpful to consider what developments would be least dispensable to present day medical practice. Certainly the discovery of "A New Kind of Rays" by Professor Wilhelm Conrad Röntgen of the University of Würzburg on November 8, 1895 would perforce be included in a list so compiled. Such discoveries as the use of cinchona which was the first important specific in therapeutics; Jenner's smallpox vaccination, one hundred years before Röntgen's discovery; the work of Pasteur and Koch in identifying the bacterial origin of disease; the recognition of insect and animal vectors in disease transmission; the introduction of antiseptic and aseptic practices in surgery and obstetrics; the initiation of surgical anesthesia by Morton fifty years before Röntgen's discovery; the development of diphtherial antitoxin; and the use of modern antibiotics all were great contributions and in large measure indispensable. Probably none of these, however, have exerted a more penetrating influence in medicine and its allied sciences than has the discovery of the roentgen ray if we take note of its present day therapeutic necessity and its vast diagnostic importance. Röntgen's discovery of the rays which bear his name was the result of unusually thorough and painstaking investigative work. Many others had produced these rays prior to his epochal observation since numerous scientists preceded him in the study and development of vacuum tubes and electrical equipment. Pfahler has related having observed the characteristic greenish glow seen upon electrical excitation of a Crookes tube in 1893 while watching a demonstration in a physics laboratory. Hertz, Geissler, Hittorf, Lenard and Crookes were among the better known and productive investigative predecessors of Röntgen in the use of these experimental devices. From 1890 to 1895 some of these workers, as well as Wiedemann and Jackson, were producing roentgen rays but regarded them as cathode rays.

Röntgen was as modest and self-effacing as he was exacting and thorough. Glasser has collected in several outstanding historical articles and books the pertinent data relative to Röntgen's work and the reaction of the world to it. The initial announcement of this astounding discovery was made prior to his intent, but in the three principal communications issued by him in late 1895 and early 1896 Röntgen presented most of the basic physical properties of roentgen rays, none of which have been proved to be erroneous. The only public address he ever delivered on his discovery was before the Physical-Medical Society of Würzburg on January 23, 1896, where he suggested that the new rays be called "x" rays thereby utilizing the algebraic symbol for the unknown. At this same time, however, von Kölliker proposed that they be named for Röntgen himself and therefore the term "roentgen rays" was introduced.

Close upon the heels of the announcement, workers on both sides of the Atlantic set about reproducing his experiments both verifying and investigating the effects of the new found rays. The fact that Röntgen first used his hand as an object of study to demonstrate the penetrability of x-rays served to accelerate their adaptation to medical use. The injurious results from prolonged and excessive exposure were likewise first noticed on the hands of the earliest workers, since it was the most readily available object with which to test the "hardness" of the tube output. The lack of any protection for the patient or the physician resulted in many

serious injuries, and ultimately to the unwitting martyrdom of some of the first investigators to employ this agent. Pfahler relates that his life was probably saved by his inadvertent use of an aluminum screen in 1899 between the tube and himself, not for protection, but to carry away any electrical currents and over which he had hung a cloth to conceal his apparatus. Russell J. Reynolds of England describes how he enclosed his early tube in a cardboard box which he then covered with a lead paint after noting a reaction on his hands. In retrospect, at least some of the softest radiation may have been thus absorbed.

The immediate period following any new development is often the most prolific and Röntgen's discovery stimulated many further investigations. The fluorescence of the early tubes suggested that naturally fluorescent substances might emit these rays, but it was fallaciously believed that the fluorescent substance gave off the rays. Becquerel in 1896 in Paris, only a few months after Röntgen published his first paper, found that compounds of uranium emitted rays and thereby discovered natural radioactivity. Two years later in 1898, Madame and Pierre Curie isolated radium, a naturally occurring radioactive isotope, the therapeutic use of which was destined to march side by side with that of roentgen rays to aid in the alleviation of human suffering. In certain lesions, the application of roentgen and radium therapy together has enabled the achievement of some of our best results.

Technical Development. Giant strides have been made in the technical development of roentgen therapy equipment from the early days of the primitive gas-filled unprotected Crookes tube, activated by Ruhmkorff or Tesla coils or a static machine, to the present day of megavoltage generators, the betatron, synchrotron, and linear accelerator. The first decade of this sixty year period was concerned predominantly with improvement of the energizing apparatus. By 1906 induction coils and static machines could produce higher voltages than the gas tubes could tolerate, and troublesome and capricious interrupters were next replaced by the "Snook interrupterless transformer" in 1907. The next great technical advance appeared in 1913 with the development of the hot cathode tube by W. D. Coolidge, after which the gas tube became a thing of the past. The Coolidge tube had a high vacuum and a tungsten target (made possible by the development of ductile tungsten by Coolidge himself). It provided the American Expeditionary Forces in World War I with the finest equipment up to that time. It was a reliable tube with consistent operation and withstood voltages up to 150 kilovolts. The first such tube seen in France was at the American Military Hospital No. 1 in 1917, and thus the Western Hemisphere had paid another installment on its scientific debt to the European continent.

The development of the Coolidge tube, followed by the introduction of autotransformer control of the primary voltage, mechanical rectifiers of disk or crossarm type, and valve tube rectifiers paved the way as clinical progress moved from superficial roentgen therapy (50–130 kv.) to medium roentgen therapy (150–180 kv.) and from medium roentgen therapy to deep roentgen therapy (200–250 kv.).

Beginning with the 1930's, several units were built entering upon the supervoltage range, *i.e.*, 500 kv. and higher. Such units at first were of experimental design, embodying various principles. Then in 1932, the large air insulated Van de Graaff electrostatic generator was first built in a hangar. In 1939 the low frequency resonance transformer appeared which was mounted in a pressurized tank of rather small dimensions. At the same time Trump devised a Van de Graaff unit similarly contained within a pressurized tank and operating at 2 million volts. These constituted an added refinement but not a great improvement clinically. The advantages of supervoltage over deep roentgen therapy were outlined as follows: (1) lesser skin

effect, (2) more homogeneous distribution with greater depth dose and less attenuation, and (3) simplification of treatment technique—fewer portals being used. In the next decade, these improvements were further explored, and definite but not revolutionary increases in five year survivals and palliation were reported. The diminished differential bone absorption in these therapy ranges was a decided advantage. Buschke and Cantril, Holmes and Schultz, Schmitz and Sheehan, Stone and Robinson, Wirth, Phillips, Leucutia, and others have contributed notably to the evaluation of supervoltage roentgen therapy results.

Kerst, in 1940, devised the betatron, which represented a departure from the direct utilization of high potential and was the first orbital electron accelerator to be used for therapy. This unit became available commercially in 1948 with an energy of 22 mev. Since then 24 mev. units have been manufactured, and in Europe a 15 mev. and a 31 mev. betatron have been built.

Even more powerful roentgen rays with energies of from 100 to 300 mev. and higher are being produced with the construction of larger and larger units.

The physical characteristics of megavoltage beams, with exit doses exceeding entrance doses and the area of maximum ionization lying deep within the phantom, will probably establish the optimally desirable energy level to lie between 15 and 30 mev. for this form of therapy.

It must be said that radiologists and physicists owe a great debt to the host of auxiliary contributors—electrical engineers, manufacturers, chemists and others who have made these outstanding advances in the development of radiation equipment possible.

Early Experiences. Claims for priority relative to the earliest use of roentgen rays in therapy have been entered by several of the pioneers in this field. It is not our purpose to assess these claims and no attempt is made to relate these developments in chronologic order.

Grubbé of Chicago had been engaged in the manufacture of Crookes tubes and similar apparatus when Röntgen's discovery was announced. He immediately began duplicating these experiments and in a short time developed a painful third degree reaction on his left hand. A physician caring for this injury suggested that a patient suffering from an ulcerated postoperative recurrent carcinoma of the breast complicated by widespread metastases be treated with this new form of energy. Grubbé treated a number of benign and malignant conditions in the period just after that, later obtained a medical degree, and reported in detail the events surrounding these early developments. He ultimately sustained extensive injuries to both hands and face, later requiring innumerable operative procedures for the removal of roentgen-induced malignancies. Many of the pioneers in the use of roentgen rays were similarly injured and aplastic anemia or leukemia appeared as other complications. In addition to the dermatitis of the hands from the fluoroscopic testing of the machines, epilation occurring from the examination of the skull suggested possible therapeutic benefits to be obtained in the treatment of skin disease. Freund in 1897 in Vienna thus epilated a large unsightly hairy nevus with reportedly good immediate results. Due to a total lack of knowledge relative to protection, a number of serious reactions occurred which served to temporarily impugn the worth of the method. The first, second and third degrees of skin reaction were described and very soon thereafter the late reactions of atrophy, telangiectasis, hyperkeratosis, warts, fissures, ulcerations and ultimate carcinomatous degeneration became known. Prejudice was evident against both the diagnostic and therapeutic use of roentgen rays, although their use in diagnosis was accepted more readily. It is surprising, in retrospect, that the deleterious effects were so widely reported early in the literature. A perusal of volumes issued about the turn of the century are replete

with references to the dangers involved, and attempts were even made to introduce legislation which would outlaw the use of roentgen rays. In the October 6, 1906 issue of the *British Medical Journal*, A. R. Robinson in discussing "Errors in the Treatment of Cutaneous Cancer," believed that roentgen-ray devices had been too widely used, even to the extent that they warranted the designation of "race suicide machines." Fortunately, the advantages were recognized and injuries reduced. It then became evident that some tumors responded unexpectedly well and that some lesions could be rendered operable despite initial inoperability. That irradiation was superior to surgery for certain types of cancers, as a palliative measure, and in controlling lesions which could not be completely eradicated, was next established. At the present time close cooperation between the radiotherapist and surgeon has steadily improved our survival rates in patients with malignant neoplasms. Indeed, it is often that the radiotherapist must adopt a "surgical frame of mind" in certain aspects of his own specialty.

Elihu Thomson demonstrated that only the portion of the body exposed developed an erythema, and Kienböck in 1900 proved that the penetrating x-rays were responsible for the effects observed in experimental animals. The histologic effects on the skin were described in 1897 by Kibbe and Gilchrist, and in 1903 aspermia was experimentally produced without injury to the skin by Albers-Schönberg. Heineke then substantiated this differential effect and believed lymphoid tissue to be the most sensitive. He deducted that leukemia would thus be amenable to treatment, being unaware that beneficial results had already been obtained by Senn. Bergonié and Tribondeau in 1904 established the chain of histologic effects occurring in rat testicles under the influence of irradiation and formulated the law which states: "Immature cells and cells in an active stage of division are more sensitive to radiation than are cells which have already acquired their adult morphological and physiologic characters." Lacassagne has studied this problem exhaustively from about 1910. He described the cellular effects occurring sequentially and postulated various mechanisms for their production. The emphasis then shifted to the supporting vascular bed, connective tissue changes, alterations in the fluidity of the system, effects on enzymatic mechanisms and other possible explanations of histologic response to irradiation. Anoxia has proved to alter radiosensitivity, and certain chemicals when administered parenterally may produce the same effect.

Dosimetry. Early in the therapeutic use of roentgen rays it became evident that some unit of dose was necessary for the specification of quantity. Various units and methods were proposed beginning with the pastille radiometers of Holzknecht, Sabouraud and Noiré and others. Quimby has reviewed in minute detail the development of radiation dosimetry and describes the use of fluorescent standards, photographic radiometers, the selenium cell intensitometer of Fürstenau and numerous other methods. Next the statement of physical factors was used for the expression of dosage after the reliability of the equipment was improved with the introduction of the Coolidge tube and closed core transformer. The practical use of erythema and epilation doses, however, was the mainstay of the clinical radiotherapist in judging the progress in treatment. Various erythema doses were proposed, such as the threshold erythema dose, skin erythema dose, skin unit dose and others. An appreciation of these units is still useful in many situations particularly when correlated with the more recent concepts of dosage. Their disadvantages primarily lie in the variation in patient response, dependence on the interpretation of the therapist, and the occasional idiosyncrasy in sensitivity. It remained for the perfection of an ionization method of measurement to place dosimetry on a more solid basis. Röntgen in his first article

pointed out that radiation would produce ionization. Franklin in 1905 described an electroscope, and Villard in 1908 designed a combination ionization chamber and electrometer scaled in Holzknecht units. He also proposed a new unit of the quantity of x-rays which he defined as "that amount which liberates by ionization one electrostatic unit of charge per cc. of air at normal temperature and pressure." This is surprising in its basic content since the "roentgen" of today represents merely refinements of this original definition.

At about this time in England the difficulty of comparing exposures from radium and other substances emitting alpha and beta particles and gamma rays was the subject of discussion. Duddell, who was then president of The Röntgen Society, thought some measurement of energy absorbed would best fill the need. This proposal, as well as Villard's, has proved farsighted since our newest efforts along these lines are in terms of the "roentgen absorbed dose" or "rad." Szilard in 1914 listed the criteria for a satisfactory ionization measuring instrument and proposed the unit of energy as that required to set free one ion and a practical unit as the mega-mega ion or 10^{12} ions. Christen at the same time suggested acceptance of the above but preferred to express the dose in terms of energy absorbed, the unit being equal to 10^{12} ions absorbed per cc. The American physicist Duane called attention to saturation potential, secondaries, etc., advocated an open air chamber and called Villard's unit the E. Other units then appeared in 1918 and 1921 such as the e (Villard) unit, R (Röntgen) unit, R (Solomon) unit, and the R (Villard) unit depending upon the country in which they were being used. Standardization of methods of measurement became increasingly imperative due to the obvious confusion. Accordingly, the Second International Congress of Radiology held in 1928 at Stockholm received a provisional committee recommendation defining the roentgen which was accepted as the international unit and designated with the small letter r. This unit has evolved to a slightly altered definition as employed today. At this meeting Failla described the prerequisites of an open air standard ionization chamber. In 1930, Taylor refined this instrument by the addition of a guarded field, making possible a portable unit. The exactness and application of the r as a measure of ionization has steadily improved with the development of air-wall thimble chambers of various kinds by Glasser, Sievert, and others. Absolute determinations of tissue dose at the surface as well as in depth became possible with Failla's extrapolation chamber, and monitor ionization chambers enabled the assurance of constancy of output from therapy machines. Contemporary efforts to improve ionization measurements have been in terms of absolute energy absorbed particularly above 3 mev. levels. The equivalence of the roentgen has been calculated in ergs per gram of tissue, and in 1953 the International Committee on Radiological Units added the rad (roentgen absorbed dose) as the most widely applicable and accurate unit. It is equal to 100 ergs/gm. Mayneord has introduced the concept of the gram roentgen or megagram roentgen to express the integral or volume dose, a problem considered by many others. This is of particular importance in radiation sickness and in the use of gamma emitting teletherapy units which have a certain unavoidable penumbra due to the rather large source size.

Further efforts have been made in this field to meet the need in expressing dosage from various types of particulate radiation and energies of higher levels. The difference in linear ionization density along the paths of penetrating particles and electromagnetic radiations has led to the concept of the RBE (relative biologic effectiveness), whereby it is hoped that energies of differing nature can be equated.

The quality of roentgen rays was first ascertained by means of the spark gap or estimated by the baneful visual examination

of the hand fluoroscopically. Benoist described the penetrometer in 1901 (B units). In 1904 Perthes made depth dose measurements leading to the use of filters in Europe. Pfahler in 1905 used a filter of leather as the most nearly tissue equivalent material. Christen proposed the half-value layer as an expression of quality in 1913, probably based on one of Röntgen's observations in his third paper in March, 1897 in which he had outlined the principle of filtration and stated that additional increments of filter hardened the beam. The desirability of homogeneity of the beam was stressed by Dessauer, who cited the use of filtration and changing target skin distance as a means of achieving this. Soon thereafter phantom measurements were begun, and the plottings of these data were named "isodose charts" by Friedrich and Glasser. Later the "equivalent spark gap," spectrometry and effective wave length were used as further means of defining quality. Determination of absorption curves and absorption coefficients then became the most reliable way of specifying the quality of a given beam.

Clinical Methodology. Despite the high degree of accuracy of the physical dose measurement which has been attained, the clinical evaluation of the biologic response to radiation has remained a difficult problem. It soon became apparent that the rate of administration of the radiation was an important consideration. A voluminous literature has appeared on the variation of intensity, fractionation, protraction and other factors influencing tissue response and clinical results. The biologic response of bean roots, Ascaris eggs, Drosophila eggs, sea urchin eggs, various embryonic tissues and other objects has enriched our fund of knowledge. Regaud's experiments in 1914 with the results of fractionation and protraction established the greater cellular sensitivity during the mitotic phase. Coutard working with Regaud applied these principles beginning in 1920 to laryngeal cancer with greatly improved results. Treatments were given early in small daily increments to a total dose determined by the end tissue changes, due in part to the reticence and occasional hostility with which this form of therapy was initially accepted by the profession. It was difficult to induce therapists to give more than palliative doses, and patients with early stages of their disease rarely were seen by the therapist. Radium was more trustfully accepted, however, and helped to bring to roentgen therapy its just integrity. Kingery and Pfahler in 1920 introduced the "saturation method," postulated a decomposition product in tissue and tried to systematize the fractionated dose technique. Other notable contributions were the Strandqvist's curve based on his experience with skin carcinoma and the study of tissue recovery relative to erythema production by Quimby and MacComb. Paterson and Garcia subsequently found close correlation between Strandqvist's curve and their observations. That much conjecture still remains is indicated by the recurring attempts to explain these phenomena. In the March, 1956 issue of this JOURNAL, three excellent articles have appeared on this subject by Allen and Freed, Andrews and Moody, and Du Sault.

Obviously the practical use of many of the newer techniques depended upon the development of finer equipment. Some of the concepts on which these techniques are based were formulated in the earliest days of roentgen therapy but because of lack of proper equipment could not be satisfactorily implemented. Rotation therapy, for example, was first described by Pohl in 1906 but enjoyed a rebirth only in recent years as an expansion of the principle of multiportal therapy. Convergent and pendulum therapy are variations of this same principle. All of these present rather difficult dosage problems. Similarly, transvaginal roentgen therapy was used as early as 1903. Grid or sieve therapy has been recently re-studied by Jolle in England, but originally was first used in a simple form many years ago. Being cognizant of these

manifestations of the fertile minds of the pioneers in this field, we are less inclined to be boastful of recent accomplishments.

Apart from the technical considerations, the strictly biologic and clinical improvement of roentgen therapy has hinged on the establishment of criteria of sensitivity, resistance, curability, and the factors altering them. It would seem that, in general, factors influencing the cellular metabolic rate are those which most affect radiosensitivity, *viz.*, oxygen concentration, temperature, vascularity and the mitotic phase. These primarily determine inherent radiosensitivity, but the stage of the disease, tissue of origin, and location of the lesion are equally or more important. Attempts to establish uniform and comparable therapeutic statistics have contributed greatly to elevate the position of roentgen therapy.

* * *

There is much to be learned from study of the early years of the development of roentgen therapy, but a look to the future can now be taken firmly based on the accomplishments of the past. If the next sixty years of radiology are as productive as the past, surely a brilliant future lies ahead. Wherein will the next significant advances lie? An undramatic but systematically thorough evaluation of megavoltage clinical effects must be accomplished as was done with the supervoltage range in the 1930's and 1940's. Possibly a chemical or hormonal preparation will increase the radiosensitivity of neoplasms. Worthwhile chemotherapeutic methods are already well established, some as auxiliary agents and others in their own right. These are some of the areas of future development. Certainly supervoltage and megavoltage roentgen-ray apparatus or gamma emitting isotopes in these energy ranges are not panacea for the treatment of malignant disease or for application to other amenable lesions, but they have contributed substantially to improve the degree of palliation, survival and cure rates.

At the close of this fragmentary recounting of some of the major steps in the history of roentgen therapy the words of Sir Thomas Browne are singularly appropriate: "Who knows whether the best of men be known, or whether there be not more remarkable persons forgot than any that stand remembered in the known account of time." A host of such men must surely stand along the byways just passed.

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A CLINICAL PROGRAM TO EVALUATE THE PRACTICAL SIGNIFICANCE OF HIGHER ENERGY LEVELS THAN THE 1-3 MEV.*

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DURING the last twenty years the radiotherapeutic armamentarium has been continuously increased by the addition of new weapons. Roentgen x-ray generators of higher voltages have been built, teletherapy units using million volt gamma-ray emitting isotopes have been developed, high energy particle fluxes have been made available from generators and reactors. Although rotation therapy is almost as old as radiation therapy, increasingly complex moving field techniques are being used.

The initial cost, the housing, and the maintenance of radiotherapeutic equipment have increased the actual cost of treatment, making the management of cancer patients a major economic problem. Although cost may be of little or no concern during the developmental phase of new forms of therapy it must eventually be considered in proportion to the clinical benefits derived by the whole population of cancer patients.

It is therefore timely to institute clinical evaluation programs designed to analyze the practical value of these newly developed tools and to determine optimal forms of external beam apparatus. Such programs can only be based on the clinical knowledge acquired by years of experience with the natural course of cancers and their response to ionizing radiation. A practical answer cannot be obtained by theorizing on potential advantages.

It is upon this premise that in September, 1951 a grant was requested from the National Cancer Institute for the purchase of a 22 mev. Betatron for the purpose of evaluating the clinical effectiveness of higher energy beams. Squamous cell carcinomas, rarely cured by conventional means due to lack of control of the primary lesion, its immediate extensions and proximal lymphatic spread were suggested as clinical material for the program. The program excluded those cancers which, although radiosensitive by their histologic nature, are not affected materially in their course due to their biologic characteristics. A comparison of methods of treatment is apt to be more accurate if made within the same institution because of the wide variations in clinical material.

As Cobalt-60 teletherapy units are a form of 1–3 mev. equipment, their potential benefits are likely to be those of the one million volt generators. These generators have been in clinical use for more than twenty years, and the physical characteristics of their beams have been carefully studied. The clinical significance of lesser skin reaction, lesser differential bone absorption, greater depth dose and lesser systemic reactions due to a decreased integral dose is fully understood. Well defined clinical impressions have been formulated as to the types of tumors in which definitive supervoltage therapy results in improved cure rates, or palliation with better tolerance. As yet no series of any type of cancer has been reported showing statistically significant differences in cure rates.

Two definite conclusions stand out in the experience of two decades with supervoltage therapy. First, those cancers, histologically radiosensitive but biologically self-determining, *i.e.*, carcinomas of the bronchus, are not affected materially in their course by the use of supervoltage therapy. [1,5,6,16,17,28] The best that can be said for such therapy is that perhaps short range palliation is achieved with somewhat

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less discomfort. This quantitatively ill-defined advantage renders those tumors unsuitable in a study of higher voltages, as obviously no further gain can be obtained. Second, there are other types of tumors, *i.e.*, tumors of the posterior third of the oral cavity and tumors of the urinary bladder, in which conventional medium voltage therapy alone or combined with interstitial gamma-ray therapy has produced a consistent but low percentage of cures. In these cases, supervoltage radiation produces an appreciable prolongation of life and increases the cure rate. This can be accomplished with greater technical ease and comfort to the patient. However, series published thus far[1,3,5,17,24,28] are too small for statistical significance. One of the major difficulties in evaluating benefits of further increase in voltage, different types of equipment in the multimillion range and moving field therapy is the lack of a quantitative base line of effectiveness of the 1 mev. level using simple conventional stationary techniques.

Two mev. roentgen-ray generators, kilocurie Cobalt-60 teletherapy units, and 22 mev. Betatrons have been in clinical use from four to ten years. As yet there are no statistical data available as to their superiority. It is the impression of Buschke and Cantril, who have had years of experience with 0.8 mev. and later with 2 mev. equipment, that there is no detectable difference in their clinical value (personal communication). This stands to reason, as a change in millimeters in the depth of the electronic build-up does not affect the skin reaction, and the depth dose is only slightly increased. With reference to the skin reaction, differential bone absorption and side scatter, the 1 mev. level is almost optimal. It is most probable that the main complication of supervoltage therapy, *i.e.*, subcutaneous and connective tissue fibrosis within the slab of tissue irradiated, will not be materially changed. The same is therefore applicable to Cesium-137 or Cobalt-60 teletherapy units which are respectively equivalent to 1 and 3 mev. roentgen-ray generators. Buschke[6] feels that it is possible to deliver with the 1–3 mev. equipment doses which are adequate for the sterilization of radioamenable tumors anywhere in the body without unbearable changes in the tissues. However, Friedman[12,13] holds the opinion that the risk of late fibrosis, inherent to stationary techniques at the supervoltage level, can be eliminated by the use of rotation techniques, and that stationary portals (one single or two parallel opposing, so attractive at the 1–3 mev. level because of the absence of appreciable acute skin reactions) ought to be abandoned.

If rotation therapy at the 2 mev. level is optimal[12,23] having solved the problem of delivering adequate doses with satisfactory volume distributions, then clinical trials using higher energy levels are unwarranted. However, a careful clinical investigation must be made to determine (1) if rotational patterns are "cancerwise procedures" for the majority of cases which come under radiotherapy care, and (2) if long range follow-up shows that late complications are eliminated.

The geometric distribution of the ionizing energy must be designed to cover the anatomic spread of the disease, and it cannot be said, *a priori*, that rotation therapy is in itself superior. If the primary tumor, its contiguous extensions and lymphatic spread can be encompassed in a rotational volume distribution, rotation therapy may be superior provided the portals are small enough to take advantage of a rotational pattern. A careful analysis of those situations commonly encountered shows that with reference to the anatomic spread of the radioamenable cancers, *i.e.*, head and neck tumors, squamous cell carcinomas of the cervix, breast carcinomas, and lymphomas, rotational techniques produce poor anatomic coverage. Only a small minority of the cases in the head and neck area and pelvis are better handled by rotational patterns. Tumors of the urinary bladder without too extensive paravesicular involvement are possibly an exception.

It should be emphasized that although the 1–3 mev. roentgen-ray generators and teletherapy units using either Cobalt-60 or Cesium-137 have equivalent physical characteristics, the geometric shape of their beams is different. Two mev. roentgen-ray generators have little, if any, penumbra, whereas teletherapy units do not have a sharp geometric beam. The M. D. Anderson Hospital's Cobalt-60 unit, which has at 50 cm. source-skin distance a minimal penumbra, has a sizable penumbra at 70 cm. source-skin distance which is the minimum collimator-patient distance to assure clearance during rotation. It has been an accepted concept that rotation therapy produces well-defined volumes of homogeneous radiation with sharp fall-off. The compounding of complete volume distributions for rotational patterns with a Cobalt-60 teletherapy unit shows that the fall-off is smooth,[4] resulting in the irradiation of large volumes of tissues to high doses, and in high integral doses within the slab of body in which the organ is located (Fig. 3 and 11). This has produced, in our experience, intolerance to treatment. Such intolerances may not occur in using 2 mev. roentgen-ray generators.[9,12]

Clinical trials of higher energy levels are warranted and the essential problem is to determine which voltages are best. Roentgen-ray generators of 4 to 6 mev. (with electronic build-up 1–2 cm. below the skin and slightly increased depth dose) should not have any revolutionary influence on the geometric patterns, and consequently should have the advantages, disadvantages, and complications of supervoltage therapy of the 1–3 mev. energy level. In considering higher energy levels, it appears that at least 15 to 20 mev. should be explored, as the electronic build-up is displaced several centimeters below the skin and the depth dose is greatly increased (Fig. 1).

The unfavorable "hot spots" in the subcutaneous tissues, unavoidable with one single or two opposing parallel portals technique at the 1–3 mev. level, can then be eliminated (Fig. 2). This in itself is a potential advantage, as this simple field arrangement often cannot be replaced by any other because of the anatomic spread of the tumors. In addition, the tremen-

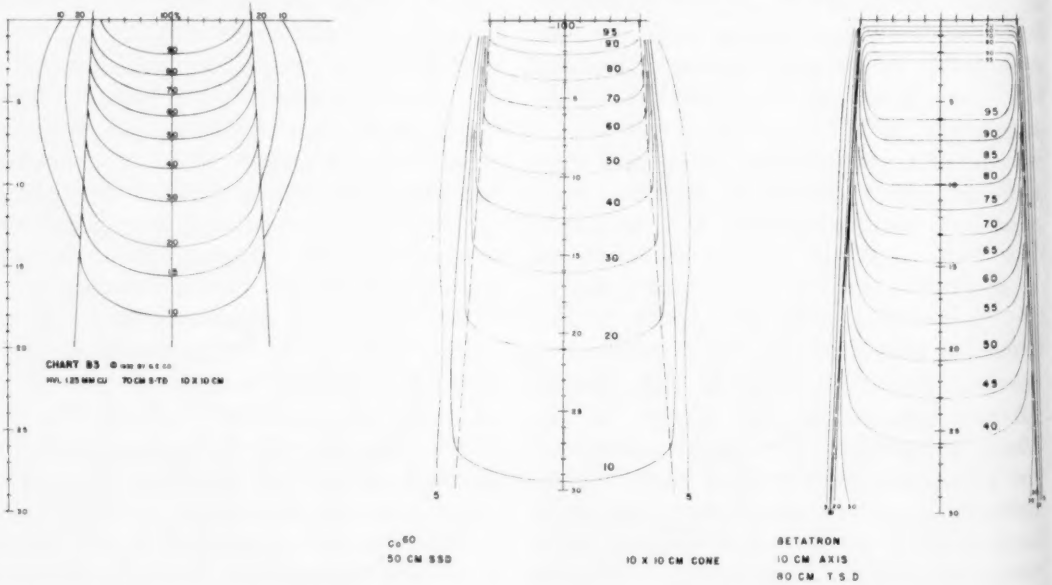


FIG. 1. The comparison of the three isodose curves brings out (1) the proportionally greater increase in depth dose from Cobalt-60 to Betatron than from 250 kv. to Cobalt-60, (2) the considerable increase in depth of electronic build-up, (3) the absence of either side scatter or penumbra with the Betatron beam.

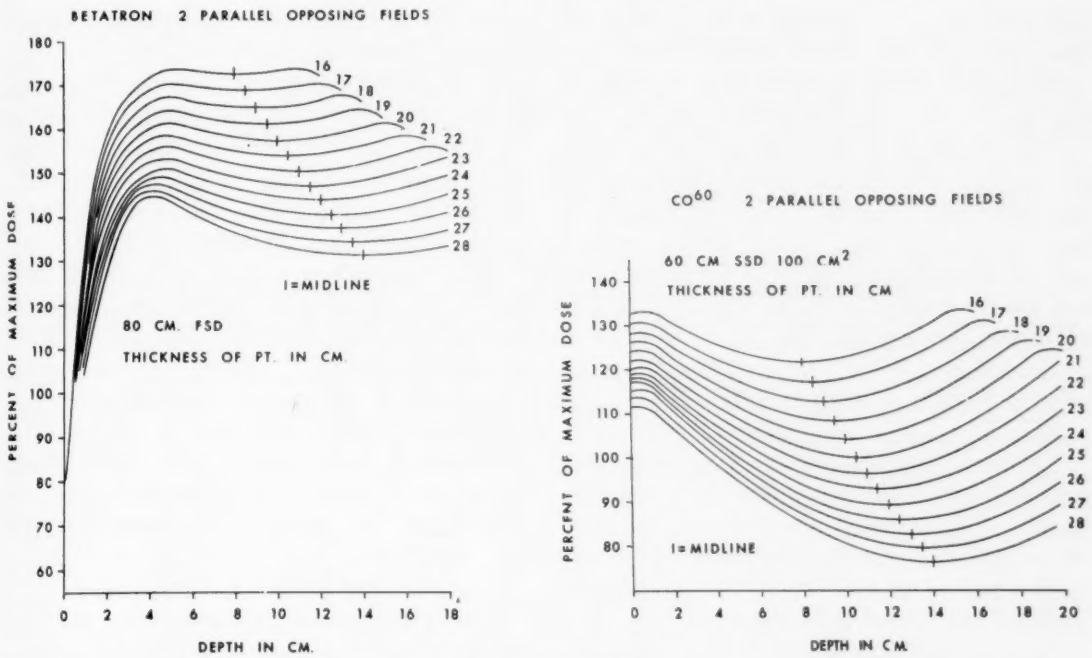


FIG. 2. The graphs represent the dose distribution for parallel opposing portals with the Cobalt-60 and the Betatron, for varying thicknesses. Only one-half of the graph has been completely reproduced as the other half is symmetrical. With the Cobalt-60, irrespective of the thickness of the part, there is always a high subcutaneous dose with a minimum at mid-distance, whereas with the Betatron the subcutaneous dose is much less than the dose through the mid-portion. It is possible that cases treated by one single or two parallel opposing portals with the Betatron may not develop later on the subcutaneous fibrosis which has been experienced using the same techniques with the 1 or 2 mev. equipment.

dously increased depth dose of the 22 mev. level permits the development of radically different types of treatment, for instance, high dose whole pelvis technique for late stages of carcinomas of the cervix. The volume distribution is optimal within the tumor bearing area and very favorable outside of it.

AIM AND CLINICAL MATERIAL OF THE EVALUATION PROGRAM

An investigation of the therapeutic possibilities of any equipment can be fruitful only if performed on a group of cancers where definitive results are obtained and the possibility of improvement exists. Patients with early squamous cell carcinomas, such as those on the lateral border of the tongue or vocal cords, are successfully treated by conventional therapy. No improvement in cure rate or in functional results is to be expected, and therefore no information as to the superiority of supervoltage therapy over other radiotherapeutic methods will be obtained. Neither can hopeless cases yield information of value. It is obvious in such cases that no form of local treatment, either surgical or radiotherapeutic, can cure or even arrest a generalized disease. The inclusion of such cases in clinical material used for testing a new type of treatment can only distort the picture.

Clinical material is therefore to be limited to those cancers which are known to be potentially curable when first seen, *i.e.*, apparently still localized to the primary site or with metastases to the proximal lymph nodes only. The cause of death in these cases is frequently the inability, with conventional techniques, either surgical or radiotherapeutic, to control the primary disease and/or the regional metastases. Cases in this category are primarily

advanced tumors of the oral cavity, all tumors of the posterior third of the oral cavity and pharynx, advanced tumors of the larynx, late squamous cell carcinomas of the cervix, and infiltrative tumors of the urinary bladder. In this group supervoltage therapy has produced slightly improved cure rates and longer arrest with less local and systemic reactions.[1,3,5,17,24,28] Squamous cell carcinomas of the esophagus, although yielding very poor results to any form of radical therapy,[7] will be included because objective symptoms and roentgenologic signs of progress are readily ascertained.

The experimental design must take full advantage of the physical characteristics of each type of equipment. With the Cobalt-60 unit either stationary portal or rotational techniques are used to their best advantage. Rotation therapy with the 22 mev. Betatron has not yet been explored.

The physical characteristics of the 22 mev. Betatron (Fig. 1) which differ substantially from the 1–3 mev. roentgen rays are: (1) a much deeper electronic build-up; (2) significantly increased depth dose; and (3) lack of side scatter or penumbra.

A well designed clinical experiment is necessary to determine whether these characteristics are only of theoretical advantage or whether they actually produce improved results.

The deeper electronic build-up may be of advantage for lesions which are best covered by one single portal or two parallel opposing portals. At times, the two parallel portal arrangement, necessary with the Cobalt-60 teletherapy unit, can have one single portal Betatron alternate (Fig. 4). If there are no palpable lymph nodes and/or if the primary is in such a location that the probable incidence of positive lymph nodes is not high, wax molds can be dispensed with, thus substantially decreasing the subcutaneous doses. Even with wax build-up, one single or two parallel opposing portals with the Betatron do not produce the subcutaneous hot spots which cannot be avoided with the Cobalt-60 (Fig. 2 and 5). Both deeper electronic build-up and increased depth dose produce a better ratio of tumor dose to dose outside of the cross-fired area in the Y-shaped arrangements of fields, as illustrated in the treatment of patients with tumors of the urinary bladder (Fig. 10). Only long follow-up will reveal whether the Betatron produces less late fibrosis.

The tremendously increased depth dose permits a departure from conventional techniques; for instance, high dose, whole pelvis techniques can be used in late stages of cancer of the cervix. The classical approach of radium therapy, supplemented by external irradiation, can be supplanted by external irradiation alone or combined with much decreased local radium therapy.

BIOMETRIC DESIGN

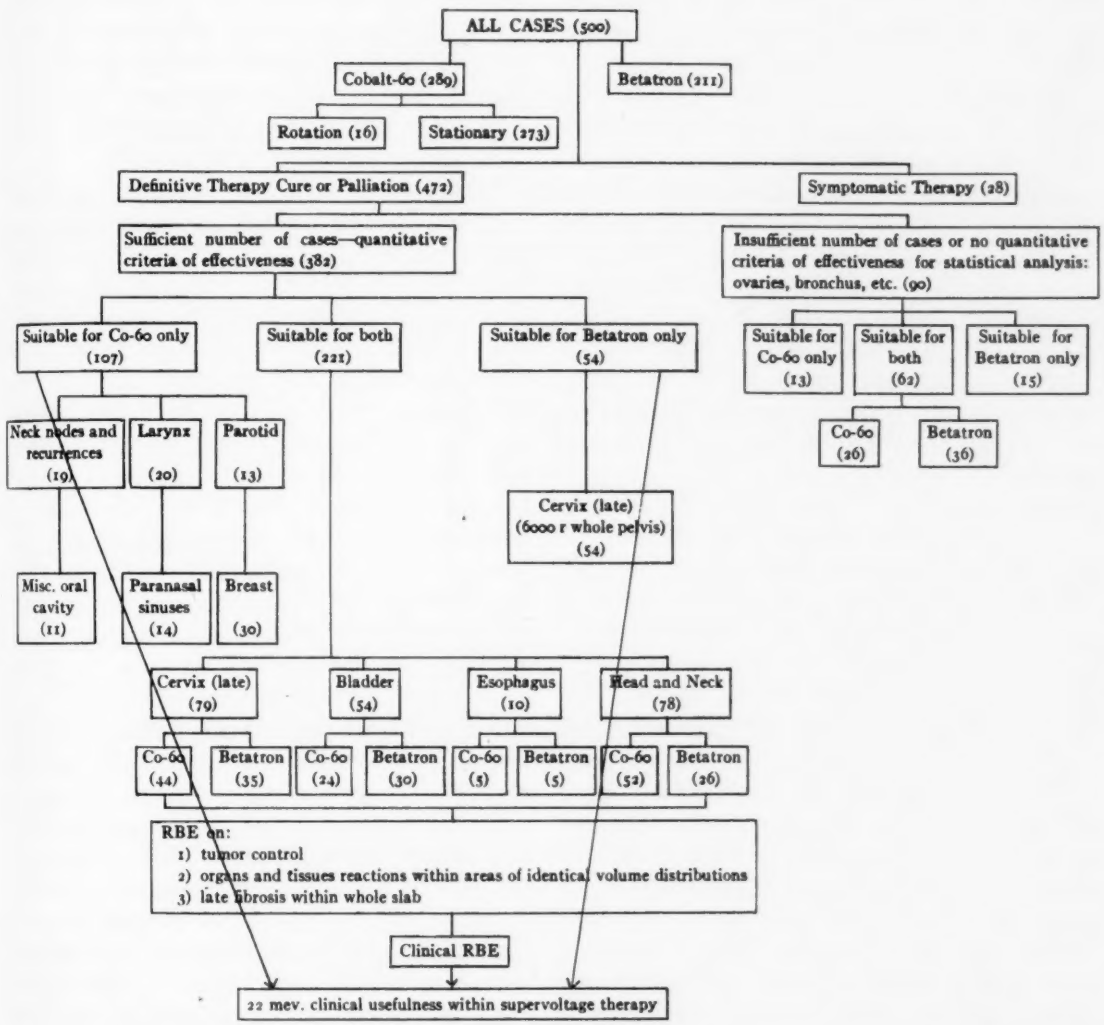
The tumors for testing the physical characteristics of the teletherapy Cobalt-60 unit and the 22 mev. Betatron must not only be suitable on the basis of their natural history and anatomic spread, but also must fulfill two other requirements:

1. They must occur in sufficient numbers so that statistical analysis is possible.
2. They must meet other criteria, such as observable local control, tolerance to treatment, possibility of associated surgery, etc., which are quantitatively recordable findings for a comparative evaluation.

All the cases treated with supervoltage radiation are then checked against this biometric design (Table 1). There is a group of cases which, for various reasons, is treated with the supervoltage instead of 250 kv. for vague symptomatic palliative therapy or where treatment was abandoned due to a fast deterioration. Obviously, no therapeutic difference could be expected between Cobalt-60 and 22 mev. Betatron, whatever temporary relief is achieved. There are tumors within the definitive therapy group which are not numerous enough for statistical analysis or which do not present quantitatively recordable criteria. The tumors which occur in sufficient numbers with quantitatively recordable criteria of effectiveness comprise

TABLE I

2-1-54 to 8-1-55



the group suitable to evaluate the clinical usefulness of a 22 mev. Betatron versus teletherapy Cobalt-60 unit, and consequently determine the place of multimillion volt therapy.

The allocation of material to one type of equipment or the other, or the suitability for both, is based on the possibility of delivering the desired tumor dose without overtaxing normal tissues by simple, duplicable, and anatomically accurate settings. The addition of sufficient thickness of wax permits all cases to be treated on the Betatron. However, if odd-shaped anatomic fields are essential for successful therapy (either to cover the disease or spare vital structures), the collimation of the Betatron beam makes its use more difficult, although a light collimator has been developed for the Betatron which increases its anatomic adaptability. There are also instances, such as tumors of the larynx, in which a wax mold interferes with the indispensable direct positioning. In cases where the skin sparing effect is paramount, such as in preoperative irradiation of the breast, the addition of wax build-up would make the treatments not only clumsy but contraindicated. The treatment of the supraclavicular and in-

ternal mammary chain lymph nodes would result in dangerous depth doses to the mediastinum and lung structures. For this group, the Cobalt-60 teletherapy unit is the equipment of choice.

There are, on the other hand, cases which would not receive an adequate tumor dose without excessive danger of subcutaneous and connective tissue fibrosis if treated with the Cobalt-60 unit. If a rotational pattern with the Cobalt-60 is a "cancerwise procedure," it is considered as an alternate possibility for the delivery of high tumor doses in thick patients. Taking into consideration the tumor dose and the thickness of the part, somewhat arbitrary diameters are taken as the limits above which cases are treated only on the Betatron.

Whenever the volume distribution is equally satisfactory with both pieces of equipment, cases are alternated. With the Betatron, there is a better ratio of tumor dose to integral dose within the part of the body where the organ is located. Follow-up of longer survivors will show if this advantage results in less undesirable fibrosis.

Tested clinical procedures such as additional treatment at the end of the delivery of the planned tumor dose to any residual disease using smaller portals, interstitial gamma-ray therapy, or surgery are continued. These clinical techniques are valuable irrespective of the energy level, having been elaborated to meet the biologic nature and the clinical course of the disease. Such additional procedures are performed regardless of the equipment used. They do not distort the evaluation of tumor regression. The ease and extent of morbidity or late complications of additional procedures, either radiotherapeutic or surgical, are, in addition, criteria of evaluation of the two energy levels.

CLINICAL RADIOBIOLOGIC EQUIVALENCE

The relative biologic effectiveness (RBE) is the specific response of biologic material to different wave lengths, other factors being eliminated. The most recent information concerning the RBE for medium voltages, 1–3 mev. and 22 mev. levels, is that the RBE is approximately 1.0 for unicellular organisms, whereas it is approximately 0.8 for total body response. This difference between the RBE for unicellular organisms and whole mammalian organisms shows the complexity of response to wave length.

In human therapy, tumors irradiated are situated in organs, which are located in regions of the body which are part of the total body. The metabolic state which varies with the integral dose reflects upon the status of the tumor bed, and therefore both on the tumor response and on the tolerance and recovery of the supporting structures. The importance of the volume factor in the tolerance of the skin, mucous membranes and organs has been long known. It has been quantitatively expressed for skin reactions in medium voltage therapy.

The clinical RBEs are the optimal volume-dose-time relationships at the different energy levels for the various clinical entities. These relationships form clinical treatment units, the components of which cannot be dissociated. Radiotherapeutic techniques cannot be transferred from one energy level to another by using one universal RBE factor. The optimal volume-dose-time relationships are somewhat different for the squamous cell carcinomas of the oral cavity and larynx, and have no common denominator with those for squamous cell carcinomas of the uterine cervix.

Based primarily on skin response, the RBE of the gamma-rays of radium and of roentgen rays of 1 mm. Cu half-value layer was determined to be 0.6. Even if, in some of the experiments, the electronic build-up component was eliminated by the use of build-up material, the radium and roentgen-ray beams were not identical, so that the volume factor was not eliminated. Grimmett[29] re-designed a roentgen tube to produce a beam geometrically identical to a teleradium unit beam. An equal number of patients with head and neck tumors were treated with identical techniques on both equipments. The teleradium unit was

used without build-up material, and the RBE on skin was found to be 0.6. The RBE on mucous membranes was placed at 0.8, using the earliest date of appearance of a fibrinous exudate on the tumor as an index of severity of mucositis. The RBE for tumor regression was considered to be approximately 1, as there was no statistical difference in the cure rate of both groups.[29]

A review of the literature shows a wide range of advocated tumor doses both for the 1–3 mev. level and the 22 mev. level. Some radiotherapists[1,3,5,6,17,24,28] give tumor doses which are not significantly different from those given at medium voltage. Others[12,15,25,26,27] give much higher doses, ranging from 6,000 r in three weeks, to 10,000 r in five to six weeks. There is as yet no study at the 1–3 mev. level equivalent to Paterson's[22] study of optimal volume-dose-time relationships for medium voltage. These optimal relationships at the supervoltage and multimillion volt levels are still to be determined.

On the basis of the ion density distribution, the RBE of Cobalt-60 and 22 mev. Betatron ought to be equal,[8] but the geometry of the teletherapy unit and Betatron beams is significantly different. This is due not only to the greater depth of electronic build-up and considerable increase of depth dose, but also to the lack of side scatter and penumbra of the Betatron beam. The influence of these differences on the volume factor is already apparent. There is seemingly an increasing difference in the severity of reactions to equal doses delivered with both beams as the volume irradiated increases. The somewhat better tolerance to the Betatron for larger volumes cannot be explained except by a more favorable ratio of tumor dose to integral dose within the part of the body involved.

The clinical experiment was started by keeping constant tumor dose and time for the same clinical entities in order to obtain information on: (1) tumor response; (2) mucous membrane reactions, acute and late; (3) whole organ tolerance; and (4) total body tolerance. Changes will be made until optimal volume-dose-time units for each equipment are obtained for the various clinical entities.

The volume-dose-time units, adopted on a trial basis, are proportionally more radical for some areas than others. For instance, the tumor doses used in the head and neck are only moderately higher, whereas the tumor doses to the whole pelvis used in carcinoma of the cervix are much higher than those used previously with conventional techniques. It should be kept in mind that even tumor doses of 6,000–8,000 r in four to six weeks are still small compared with interstitial or intracavitary gamma-ray therapy doses, where the base line dose is 7,000 r in seven days.

HEAD AND NECK TUMORS

Tumors of the head and neck present a unique opportunity to follow, by direct inspection and palpation, the following: (1) response of the primary tumors; (2) response of the metastatic nodes; (3) mucous membrane reactions, acute and late; and (4) increased local control and cure rate.

Early or moderately advanced tumors of the anterior two-thirds of the oral cavity are best handled by interstitial gamma-ray therapy alone, or combined with moderate doses delivered by external beam. Early squamous cell carcinomas of the vocal cords ought to be treated with medium voltage roentgen rays, until optimal techniques are established for supervoltage therapy.

Supervoltage therapy offers a possibility for improved cure rates in advanced tumors of the oral cavity, all tumors of the posterior third of the oral cavity, and all tumors of the pharynx, with the exclusion of early tumors of the nasopharynx which are well handled by conventional means. It is in the group of tumors of the posterior third of the oral cavity and oropharynx that previous authors[1,3,5,24,28] have had the impression that supervoltage therapy is of value. However, the series treated were too small for statistical significance.

The tumors of the paranasal sinuses,

which in our institution are handled by radical surgery followed by irradiation aimed primarily at delivering maximum doses to the ethmoid region and the pterygoid fossa, can only be treated with the Cobalt-60 unit. The same applies to the more extensive tumors of the laryngopharynx (due to the necessity of anatomic fields and no wax mold interference), and to malignant tumors of the parotid fossa, due to the risk of brain damage if wedge filter techniques are not used.[11]

Rotation therapy has been tried whenever the natural history of the disease and its anatomic spread make it a "cancerwise procedure," for instance, in tumors of the retromolar trigone and anterior faucial pillar. Due to the smooth fall-off of the dosage extensive mucous membrane reactions covering unnecessarily large areas of the oral cavity were produced, and the technique was abandoned (Fig. 3*B*). Rotation therapy for nasopharyngeal tumors has resulted in slow healing mucositis and excessive atrophy of the soft palate due to high central doses unavoidable if

Fig. 3. (*A*) Patterns for nasopharynx: two parallel opposing portals with the Cobalt-60, two parallel opposing portals with the Betatron and almost complete rotation with the Cobalt-60 (to minimize penumbra, the distance has been shortened but the post of the chair is in the way). The Cobalt-60 pattern has bilateral hot spots in the subcutaneous tissues and the temporal-mandibular joints, whereas the Betatron pattern has the maximum dose on the nasopharynx and the retropharyngeal lymphatics. To deliver, with rotation, a tumor dose of 6,000 r in 6 weeks to the retropharyngeal lymphatics, the nasopharynx itself received between 7,000 and 7,500 r. Cases treated in that fashion have shown marked delayed epithelitis, whereas in the conventional treatment with the 250 kv. the zone of maximum dose covers both the nasopharynx and the retropharyngeal lymphatics, and 6,000 r in six weeks produce mucositis, which heals in four to six weeks.

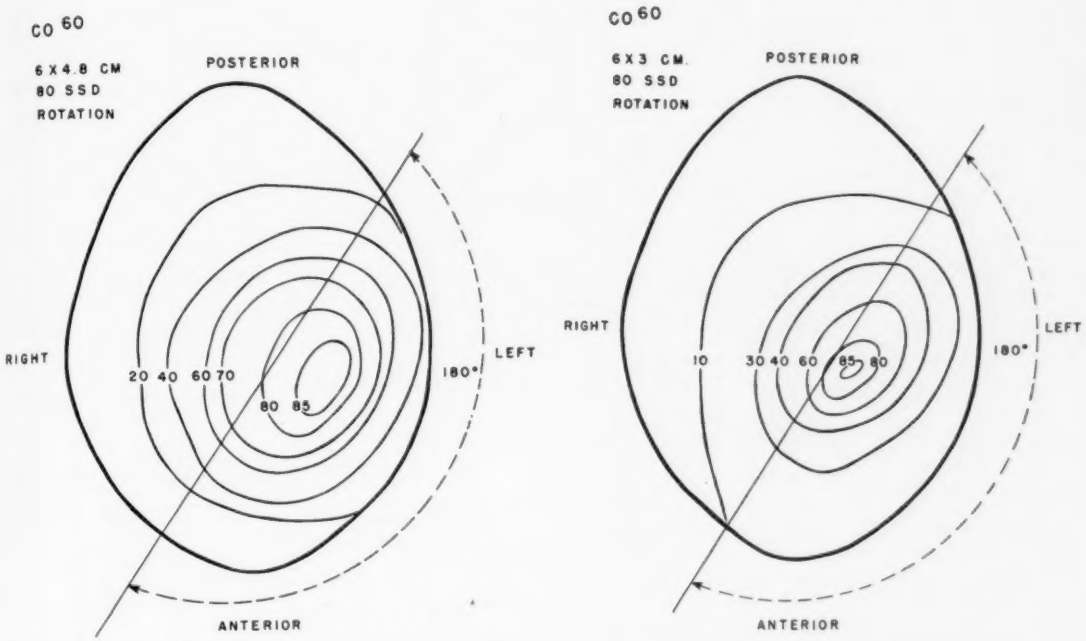


Fig. 3. (*B*) A 180° rotational pattern for a retromolar trigone tumor. On one side of the picture, a 4.5 cm. wide portal is used, on the other, a 3 cm. wide portal to see if a smaller portal would produce a more sharply defined volume distribution. There is, in both instances, smooth fall-off and in order to deliver an adequate minimal tumor dose, a great part of the oral cavity gets a high dose. In several cases the mucositis has been very severe and generalized.

an adequate dose is to be given to the retropharyngeal lymph nodes (Fig. 3*A*).

In advanced tumors of the oral cavity and tumors of the posterior third of the oral cavity and pharynx, bilateral lymphatic involvement is the rule. Clinical planning must include not only the primary tumor but the proximal lymphatics, and at times all the lymphatics of the neck, if the nodes are clinically involved. Consequently, one single portal or two opposing parallel portals must be used, irrespective of the risk of late fibrosis.

If a tumor is grossly asymmetrically located, a volume distribution with a decreasing gradient towards the contralateral side, where the disease is in its microscopic stage and therefore more radiosensitive, is best. When the tumor is closer to the midline, one single portal with the Betatron can be used (Fig. 4), or two parallel opposing portals with weighted given doses with the Cobalt-60.[11] For midline tumors, two opposing parallel portals are used with both Betatron and Cobalt-60 (Fig. 5). For irradiation of the lymph nodes, wax build-up is usually necessary with the Betatron (Fig. 5 and 6).

The volume distributions of the Betatron and Cobalt-60 cases are close, but not quite identical (Fig. 4 and 5). Subcutaneous homolateral or bilateral hot spots cannot be avoided with Cobalt-60 (Fig. 2). With the Betatron, the tissue dose is uniform throughout if a wax mold is used, otherwise less in subcutaneous tissues. If one single field is used with the Betatron, instead of two parallel opposing fields with the Cobalt-60, there is less risk of late fibrosis.

If there is evidence or heavy suspicion of residual tumor, additional radiation is given at the end of the delivery of the planned tumor dose by either using smaller portals, or by interstitial gamma-ray therapy or rotation technique. Radical neck dissection or commando type of operation are also performed in the weeks following treatment, depending upon the evolution of the primary tumor and the status of the neck lymph nodes.

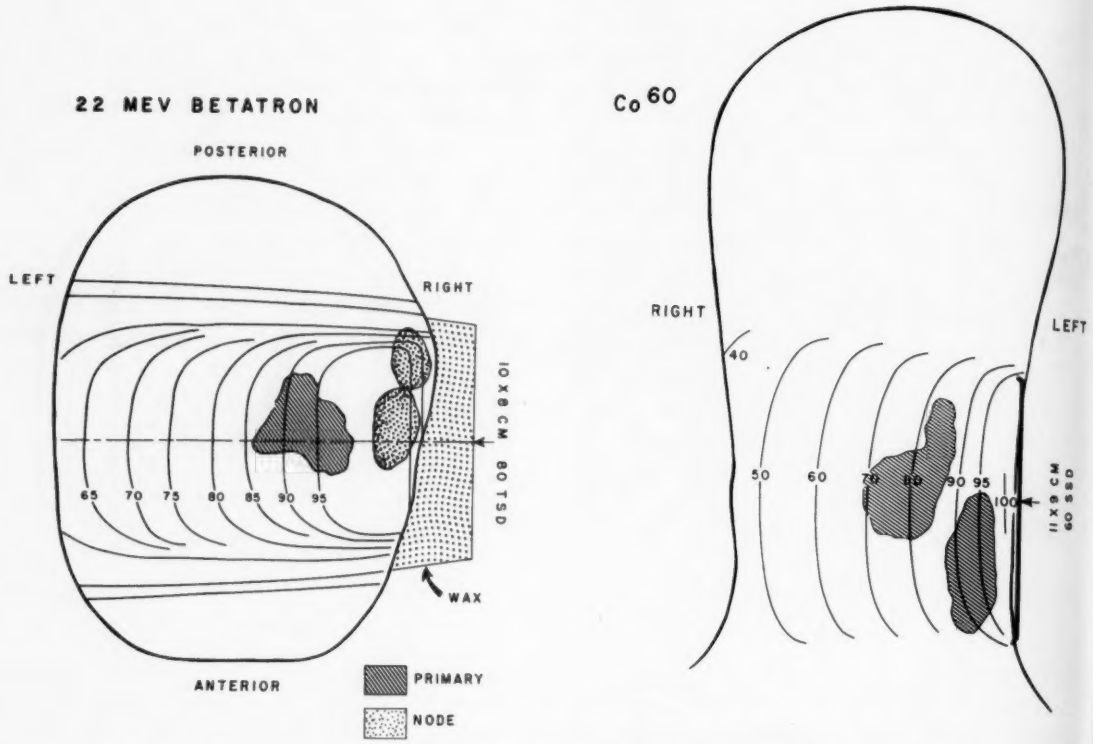
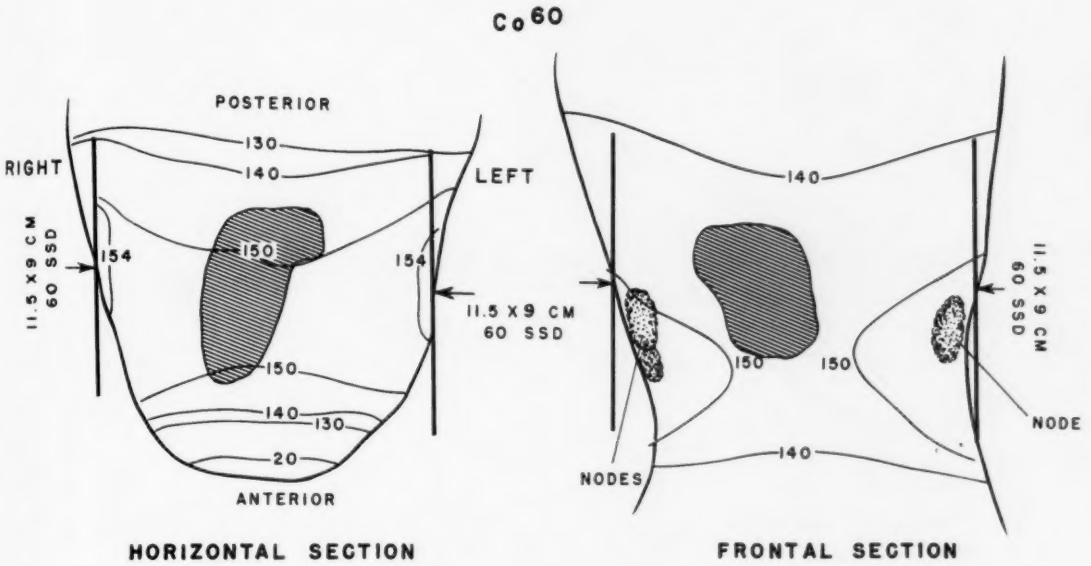


FIG. 4. (*A*) Volume distributions of cases treated with one single portal, on the left with the Betatron and on the right with the Cobalt-60 for large tumors of the tonsils with unilateral neck lymph nodes. With the Betatron there is necessity of adding a wax mold and one sees that there is a variation in tumor dose of only 15 per cent for the neck lymph nodes and the primary. With the Cobalt-60 there is a ratio of 100 to 70 per cent and the single portal technique is usually not adequate. It was used in this instance because the patient previously has had another primary lesion in the glossopalatine sulcus on the opposite side.

FIG. 4. (*B*) Patient with the wax mold in place.

A basic tumor dose of 6,000 r in four weeks had been decided upon for lesions which did not require more than 80 sq. cm. surface coverage, except for tumors of the laryngopharynx (5,500 r in four weeks for vocal cords and 6,000 r in six weeks for extrinsic larynx). For lesions requiring a coverage of more than 80 sq. cm., the time was lengthened depending upon circumstances, particularly if the laryngeal structures were in the region of high dose. A modified Baclesse technique has been used in a variety of circumstances where long protracted treatment is essential. For instance, extensive ulcerating tumors of the pharynx were treated in about 50 days, starting with low doses, increased as conditions permitted.

The degrees of intensity of mucositis and tumor regression have already been charted in 51 cases treated with the Cobalt-60 and 29 cases treated with the Betatron. A dose



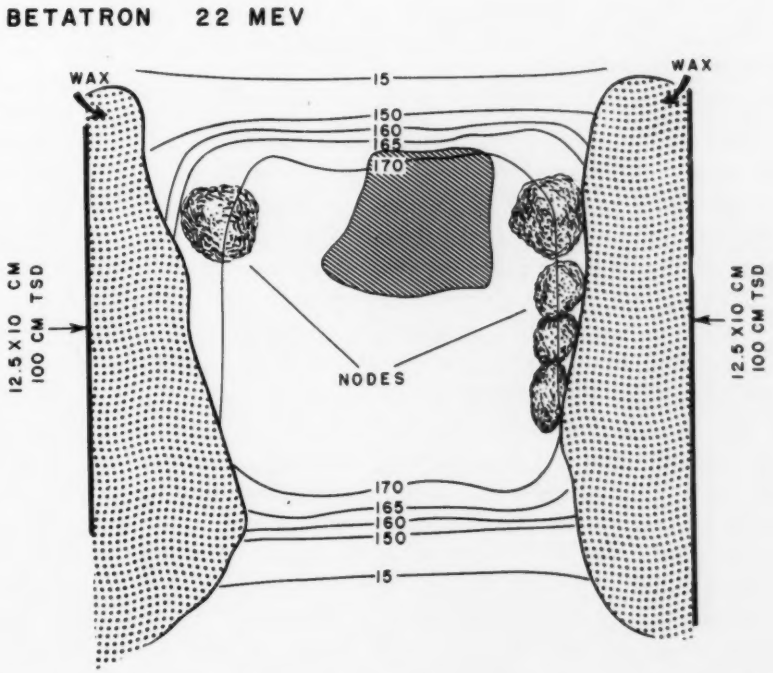


FIG. 5. (*A*) Comparison of the volume distribution of two similar cases of tumors involving the whole tongue, with bilateral neck nodes. In the Cobalt-60 case there is a slight decrease of the dose in the midline, but on the Betatron it is homogeneous. However, the two volume distributions are close.

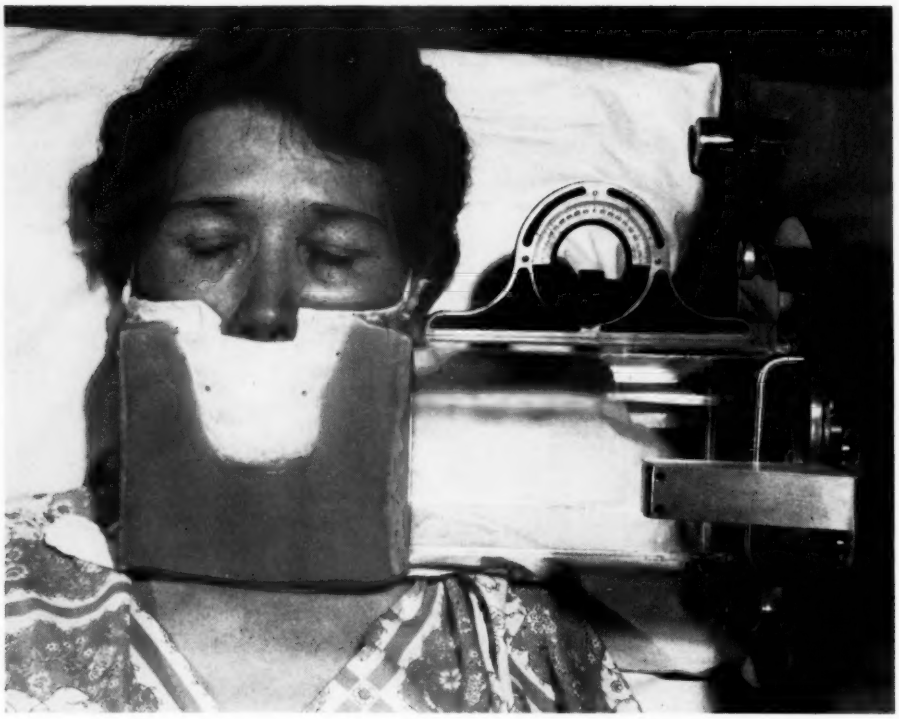


FIG. 5. (*B*) Patient being treated with wax mold. Such treatment, covering the whole lower half of the oral cavity and the neck to the level of the clavicle to include extensively involved neck nodes, is remarkably well tolerated with the Betatron.

of 6,000 r delivered in four weeks to the oropharynx with the Betatron or the Cobalt-60 produces a confluent epithelitis (Fig. 7), which reaches its peak in 12 to 14 days, remains unchanged for the next two weeks, and then heals in two to four weeks. A dose of 6,000 r delivered in five weeks produces a studded to occasionally confluent epithelitis and a dose of 6,000 r delivered in six weeks produces marked reddening of the mucosa to occasionally studded epithelitis. It has been found that using one single portal with the Betatron or Cobalt-60, these various degrees of epithelitis are graded from the homo- to the contralateral side with variations in doses of about 10 to 15 per cent (Fig. 8). The individual variations are not as marked as often stated.

In the cases treated with 6,000 r in four weeks (22 on the Cobalt-60 and 26 on the Betatron) both the mucositis and tumor regression graphs are similar. The number of cases treated on the Betatron with 6,000 r in five weeks and 6,000 r in six weeks is not sufficient for comparison for the dose-time relationship. If the doses are converted to rads, the 22 mev. rad is seemingly more effective as the same effect is produced by 5,900 (Cobalt-60) rads and 5,300 (22 mev.) rads.

A true randomization is impossible as varying extensions and lymph node involvement make individual cases unsuitable for one type of equipment or the other. The criteria for evaluation are: (1) control of the primary tumor; (2) control of the metastatic neck nodes included in the beam directed at the primary; (3) mucous membrane reactions, acute and late; (4) life span with better evaluation of local control (in the head and neck area one can dissociate the failures due to distant metastases only); (5) late fibrosis; (6) possibility of associated surgery in the form of radical neck dissection alone or so-

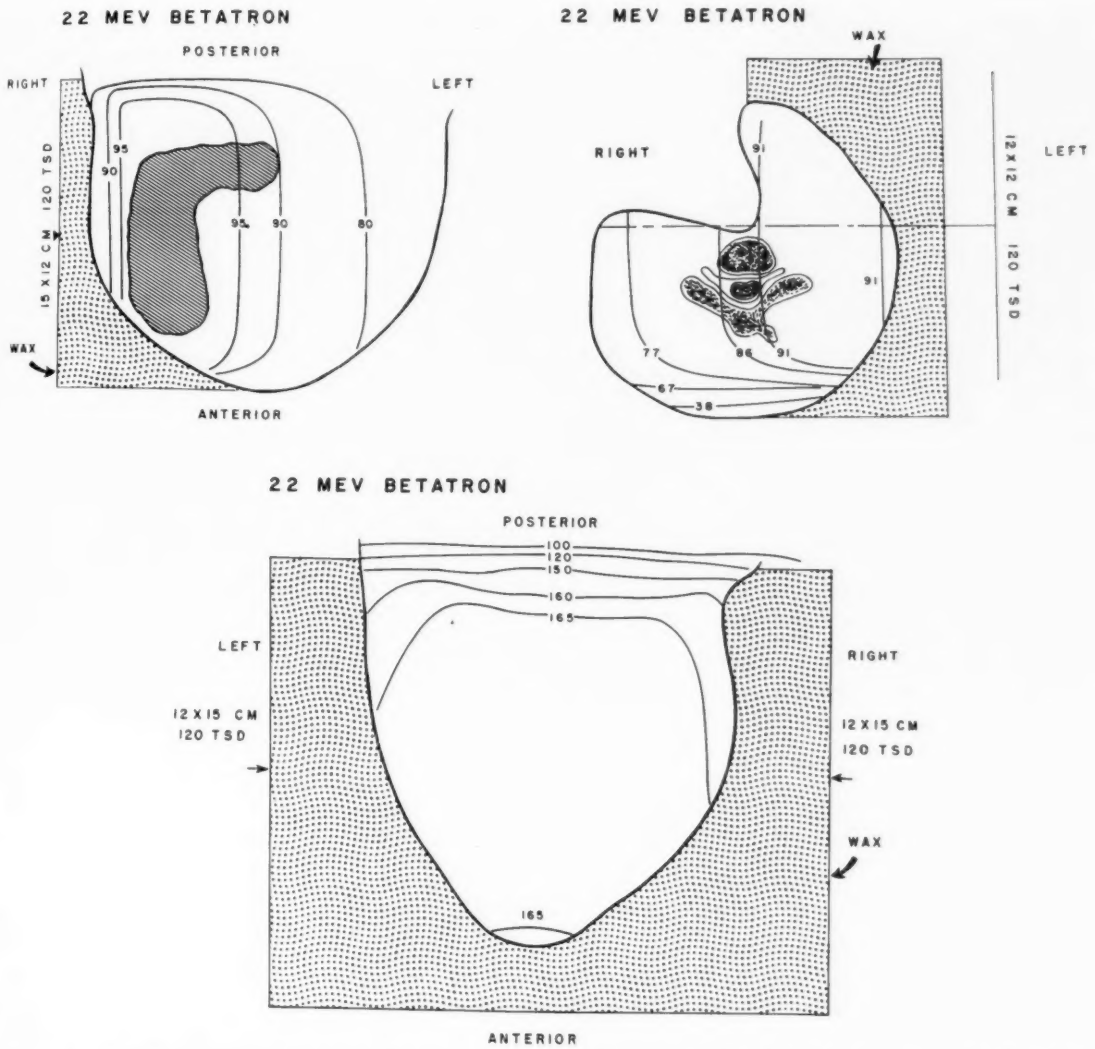


FIG. 6. (*A*) Circumstances where the Betatron can be of advantage in head and neck tumors. In the upper left corner very advanced tumor which when first seen involved the whole thickness of the buccal mucosa anteriorly to the commissure, having extended into the maxillary antrum as demonstrated by roentgenogram. Complete trismus prevented examination of the back of the oral cavity, but as the tumor regressed it was then seen that the retromolar trigone, the tonsillar fossa, the soft palate and the base of the tongue were involved. It was estimated that the longest diameter of the tumor was about 10 cm. One single portal was used covering not only the primary lesion but also the upper part of the neck where there were positive lymph nodes in the submaxillary, digastric and precarotid regions. A tumor dose of 7,100 r was delivered to the whole area in five weeks, and additional 1,500 r was given to the primary tumor through a reduced portal. Two half value layers of lead were used to shield the laryngeal structures. This proved to be efficient, as very little reaction appeared in the larynx. In the upper right corner, tumor involving the pyriform sinus and the pharyngeal walls. A laryngopharyngectomy and right radical neck dissection were performed. The surgical specimen showed tumor near margins of excision and diffuse metastases to tissues of the neck. One single portal was used on the Betatron with sufficient thickness of wax to produce full electronic equilibrium in the left neck lymph nodes, yet resulted in a very uniform dose throughout. A dose of 6,000 r was delivered in five weeks with minimal reaction. Later plastic reconstruction was carried out, successfully. At the bottom a case of one stage bilateral neck dissection for extensive bilateral lymph node involvement (some being fixed to the periosteum of the mandible). Surgery showed involvement of the lymphatics of the lower poles of both parotids and disease was left in these regions. The lower half of the face and the whole neck were given 6,000 r in four weeks.

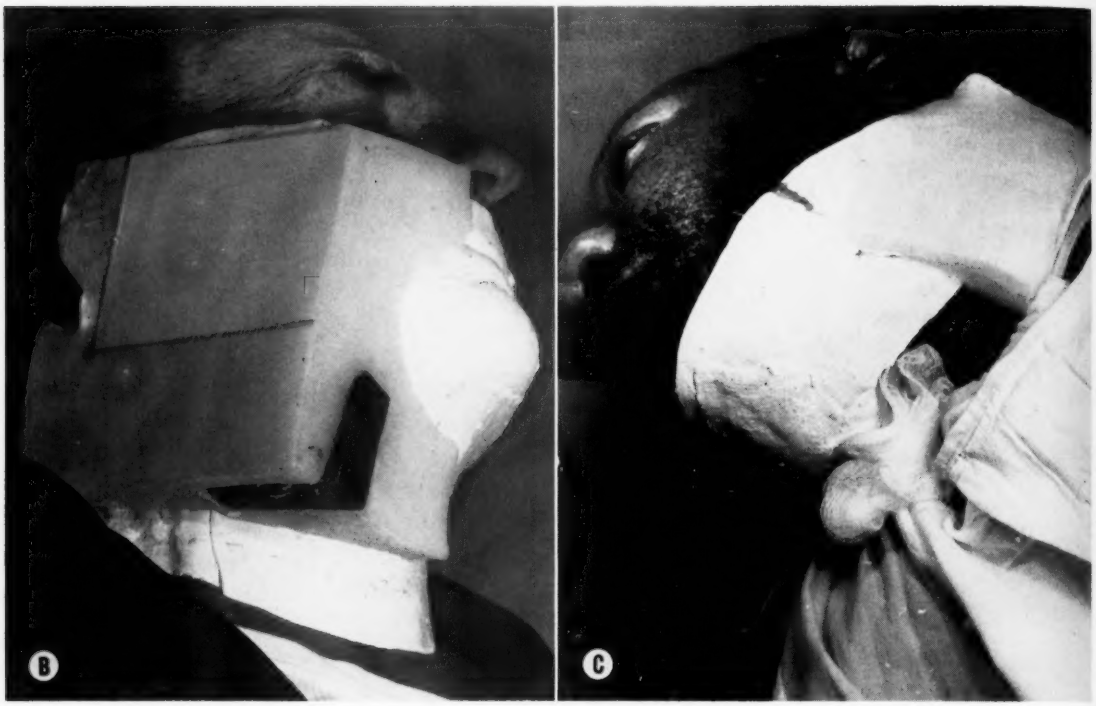


FIG. 6. (*B*) Wax mold with partial shielding of the larynx in the buccal mucosal tumor case. (*C*) Wax mold for the patient having had the laryngopharyngectomy and radical neck dissection.

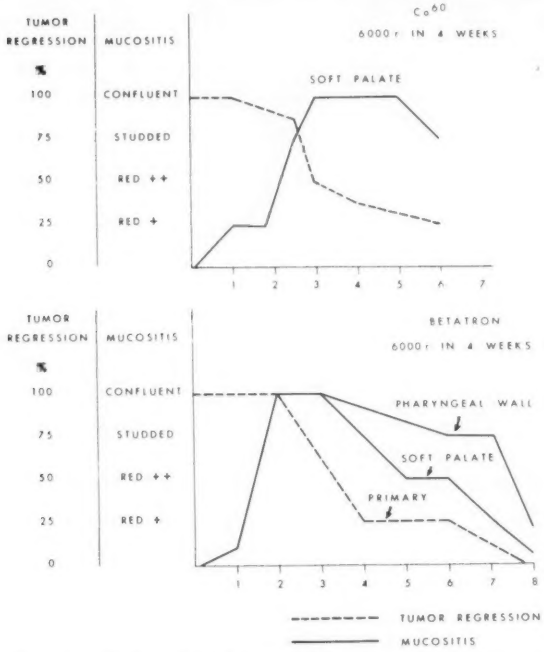


FIG. 7. (*A*) Graphs of mucositis in 2 cases of tumors of the tonsillar fossa, 1 treated with the Cobalt-60 and the other with the Betatron. It is obvious that the time of development of the confluent fibrinous mucositis and the peak are the same. There may be a slight difference in the healing slope.

called "commandos," thus testing the difference in tolerance of mucous membranes and skin; and (7) better tolerance to added gamma-ray therapy.

Seventy-four cases, 53 on the Cobalt-60 unit and 21 on the Betatron, of extensive oral cavity and oropharynx lesions have already been treated according to this program with a minimum of one year follow-up. Tumor doses have ranged from 6,000 to 7,000 r in four to six weeks, with additional interstitial gamma-ray therapy at the end of treatment whenever indicated. Regression of the primary lesions, as determined by the status of the patients when last seen, was obtained in 90 per cent of the cases even in the more advanced stages. In many instances, due to old age, complications or distant metastases the patient did not survive more than a few months and therefore the regressions cannot be construed as evidence of a permanent sterilization. One can, however, state that the incidence of primary regression is much higher than in similar groups of

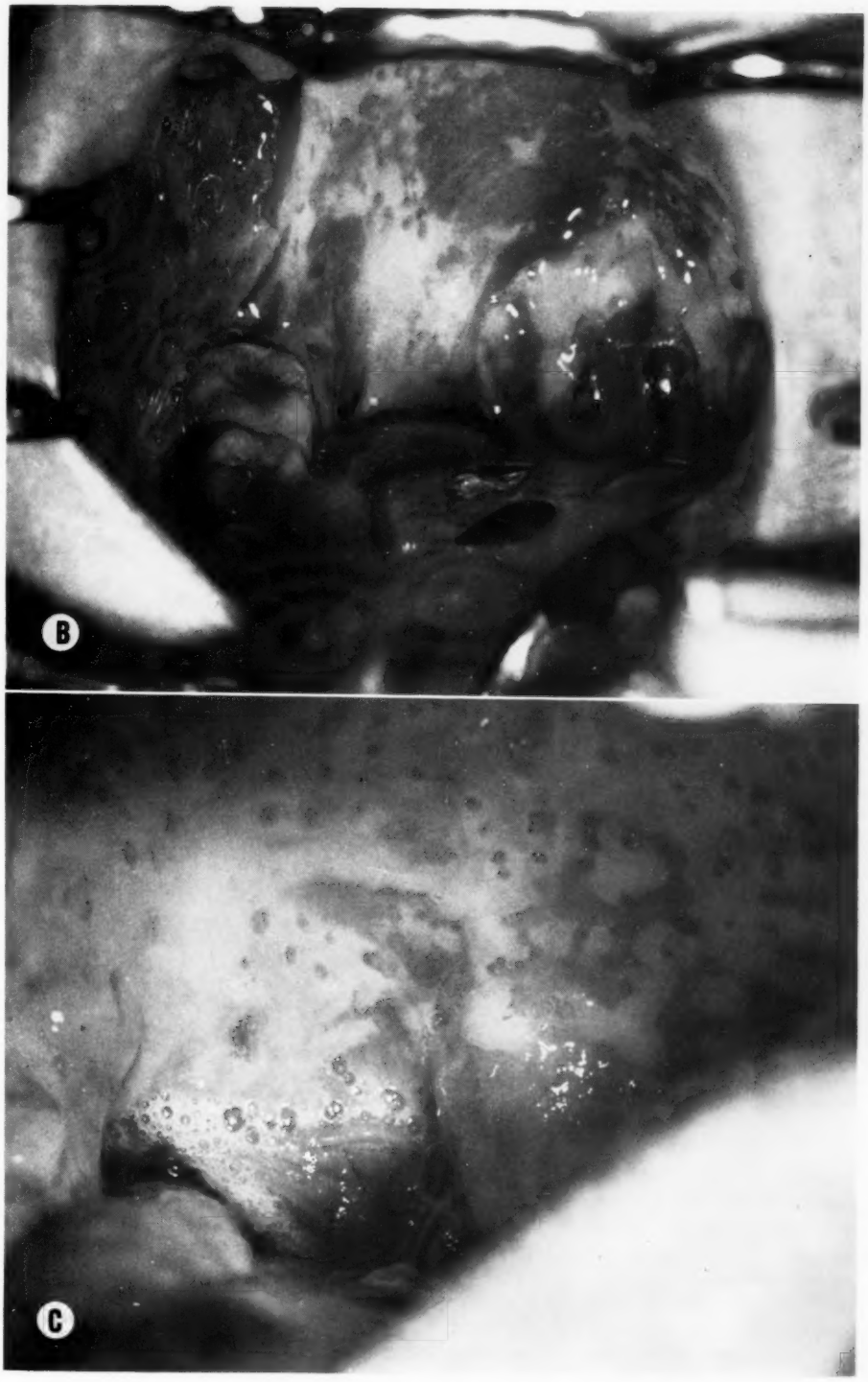


FIG. 7. (*B* and *C*) Confluent mucositis at the third week for the Cobalt-60 case and the Betatron case, respectively.

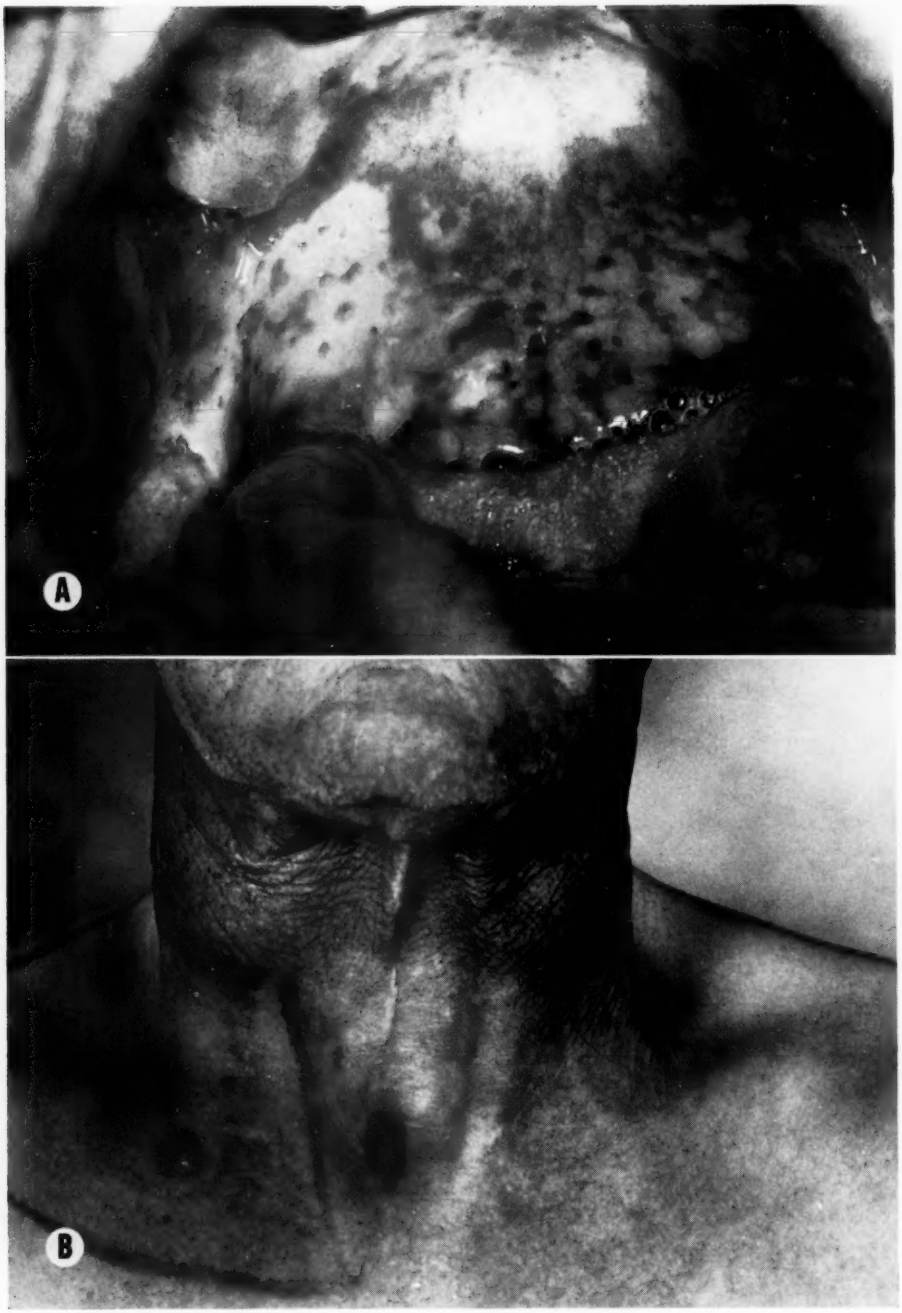


FIG. 8. (*A*) Patient having had a laryngectomy for squamous cell carcinoma of the vocal cord in the past and having now developed a second primary tumor in the right tonsillar fossa. The patient was treated with one single portal with a sufficient thickness of wax to bring the entrance skin dose at 80 per cent. The right retromolar trigone, tonsillar fossa, and adjacent part of the soft palate were approximately in the 95 per cent curve, the midline in 90–85 per cent, and the opposite retromolar trigone about 85–80 per cent. The exit dose was 75–80 per cent. One sees that there is a mucositis pattern ranging from confluent exudate on the right retromolar trigone and adjacent portion of the soft palate to studded exudate on the soft palate on both sides of the midline, and marked redness only on the left retromolar trigone. Several cases treated with either a single portal on the Betatron, or weighted opposing portals on the Cobalt-60 unit have shown that a difference in dose of about 15 per cent results in a gradation from confluent fibrinous epithelitis to marked redness. (*B*) Exit and entrance skin reaction is the same. The exit reaction covers the same surface as the entrance one, as expected because of the lack of divergence and penumbra of the Betatron beam. Similar cases treated with one single portal on the Cobalt-60 unit show a much larger exit area and gradation of skin reactions due to the gradient of dosage rates at the periphery of the Cobalt-60 beam. The right supraclavicular area was treated on the 250 kv. equipment.

cases treated with conventional techniques. The incidence of clinically positive lymph nodes in lesions of the base of the tongue was 90 per cent, and in lesions of the tonsils 60 per cent. A high incidence of clinical disappearance of the palpable lymph nodes was obtained. In 14 cases a radical neck dissection was performed following the radiation therapy, and the lymph nodes included in the beam covering the primary lesion were found sterilized in more than 50 per cent. The healing of the wound was very satisfactory and almost uneventful in the Cobalt-60 cases, but some definite delayed healing appeared in the ones treated with the Betatron. This is easy to explain, because the addition of a wax mold brings the skin in the dose of maximum ionization. Now only the cases treated on the Betatron are considered as not needing a wax mold.

The preliminary impression is that a tumor dose of 6,000 r in four weeks with additional radiation, either in the form of a gold grain implantation or small field therapy if tumor is still clinically present, is very effective. This dosage should be reserved for cases where one aims at cure and is only justified if the longevity of the patient is sufficiently good. In older patients, 75 years old or more, discomfort and nutritional difficulties are too much of a biologic trauma. In those instances a dose of 6,000 r in six weeks is better tolerated and although perhaps not bringing about as many permanent sterilizations, seems satisfactory for palliation. Breakdown of the mucous membrane at the inner angle and anteriorly along the inner aspect of the jaw is not uncommon. This complication can either be handled conservatively if the bone does not become infected, or by resection of the bone if necessary.

It is possible that if the surface coverage is more than 60 sq. cm., one should increase the time to five weeks even when cure is attempted. Greater number of cases with longer follow-up will be necessary to arrive at a better evaluation.

THORACIC CAGE

At first, the squamous cell carcinomas of the thoracic cage seem to be ideal tumors for the evaluation of higher energy beams because adequate tumor doses can be delivered with good tolerance. Results with conventional therapy are so poor that any new method is welcomed. However, two decades of extensive radical surgical approach to bronchogenic carcinomas have taught us that the biologic nature of the disease is such that when first diagnosed it is already widespread in the majority of cases. It is also well established that, whenever operable, the treatment of choice is surgery. This leaves for radiotherapeutic management those cases which are very advanced and almost always generalized. It is therefore not surprising that, irrespective of the radiation radicalism and the techniques used, including supervoltage therapy, the results have not been appreciably different from those obtained with medium voltage roentgen rays. Several authors[1,3,16,17,28] have reported extensive series in which the best achieved with supervoltage therapy is some degree of palliation with perhaps somewhat less discomfort. It is therefore evident that this group of cancers is totally unsuited for the evaluation of any other form of supervoltage therapy, as nothing short of a systemic therapeutic agent can materially change their course.

Squamous cell carcinomas of the esophagus have also been, for the last twenty years, the object of very aggressive radical therapy, using all the possible armamentarium both of modern surgery and modern radiation therapy. Multiple convergent portals, with great care of planning and beam direction, rotation therapy with fluoroscopic control, or supervoltage therapy have been used whenever available.[1,3,5,16,17,20,28] The extensive surgical approach has disclosed that squamous cell carcinomas of the esophagus, like bronchogenic carcinomas, are usually diagnosed after distant spread is present. Comparison of surgical and radiotherapeutic results using the best of both disciplines

has shown striking parallelism in survival rates with extremely few patients alive after even a few months.[7] It has become evident that, with the exception of a few early cases, there is no way to change the long range course of the disease. A careful analysis of results and complications of radiation therapy in carcinoma of the esophagus has shown that the re-opening of the lumen is the best palliation that can be offered, and is best achieved by irradiating only the visible tumor without excessive tumor doses.[5,6,20] Nielsen's results using rotation therapy with the 180 kv. equipment under fluoroscopic control, limiting the field of irradiation to the visible portion of the tumor without attempting to include long segments above and below visible cancers and the mediastinal lymph nodes, are yet to be surpassed.

It has been decided to include tumors of the esophagus in this comparative analysis of Cobalt-60 and Betatron although little comparative value is expected. There is at least one objective finding of value to the study—restoration of and duration of swallowing. Following the experience of other radiotherapists that excessive tumor doses result only in more complications and less palliation[5,6,28] tumor doses of 6,000 r are delivered in six weeks if the tumor is less than 7 cm., as measured on the esophagram; 5,500 r or even 5,000 r are delivered in six weeks if the tumor is longer than 7 cm. Two parallel opposing portals are used (Fig. 9), the cases being alternated on the Betatron and Cobalt-60 if the anteroposterior diameter is no more than 22 cm. Above this figure all cases are treated on the Betatron. Three or four portal arrangements have produced, at least in our hands, lung complications. The danger of late spinal cord damage in a group of patients who will probably all be dead within a few months is of less concern than severe, immediate radiation pneumonitis which, at times, is fatal.

The criteria for evaluation are: (1) life span; (2) restoration of normal swallowing; (3) duration of normal swallowing; (4) incidence of perforation; (5) radiation myelitis; (6) general fibrosis within the slab treated.

So far the cases of esophageal cancer which have come under our care have been extensive and the results extremely disappointing. If this trend continues, no information at all will come out of this section of the experiment, except that it confirms the extremely poor prognosis of such tumors.

URINARY BLADDER TUMORS

Improved results with better tolerance to treatment have been reported with supervoltage therapy in tumors of the urinary bladder.[2,5,28] This group is therefore suitable for evaluation of 1–3 mev. versus 22 mev. levels.

Early non-infiltrating tumors are best handled by local means consisting of electrocoagulation, partial cystectomy, and interstitial or intracavitary gamma-ray therapy. The tumors which have deeply infiltrated through the bladder wall, with paravesicular involvement often demonstrable by bimanual palpation under saddle block or general anesthesia, are no longer suitable for these local forms of treatment and can only be handled by external beam therapy. In our series, most cases have had multiple previous local treatments, including segmental resections. We have found that in patients having had a suprapubic cystostomy and also in obese patients without previous cystostomy, there is an anterior overhang of the urinary bladder. A three field arrangement, one anterior and two posterior oblique portals, produces a volume distribution which covers the whole bladder ideally. Changes in the size, position, and tilt of the portals permit paravesicular masses to be fitted within the volume distribution. Checking the coverage of tumors with the Cobalt-60 unit or the Betatron is easily accomplished (Fig. 10), and treatments are therefore accurate. If there is massive paravesicular involvement, reaching the pelvic wall, two opposing parallel portals are used.

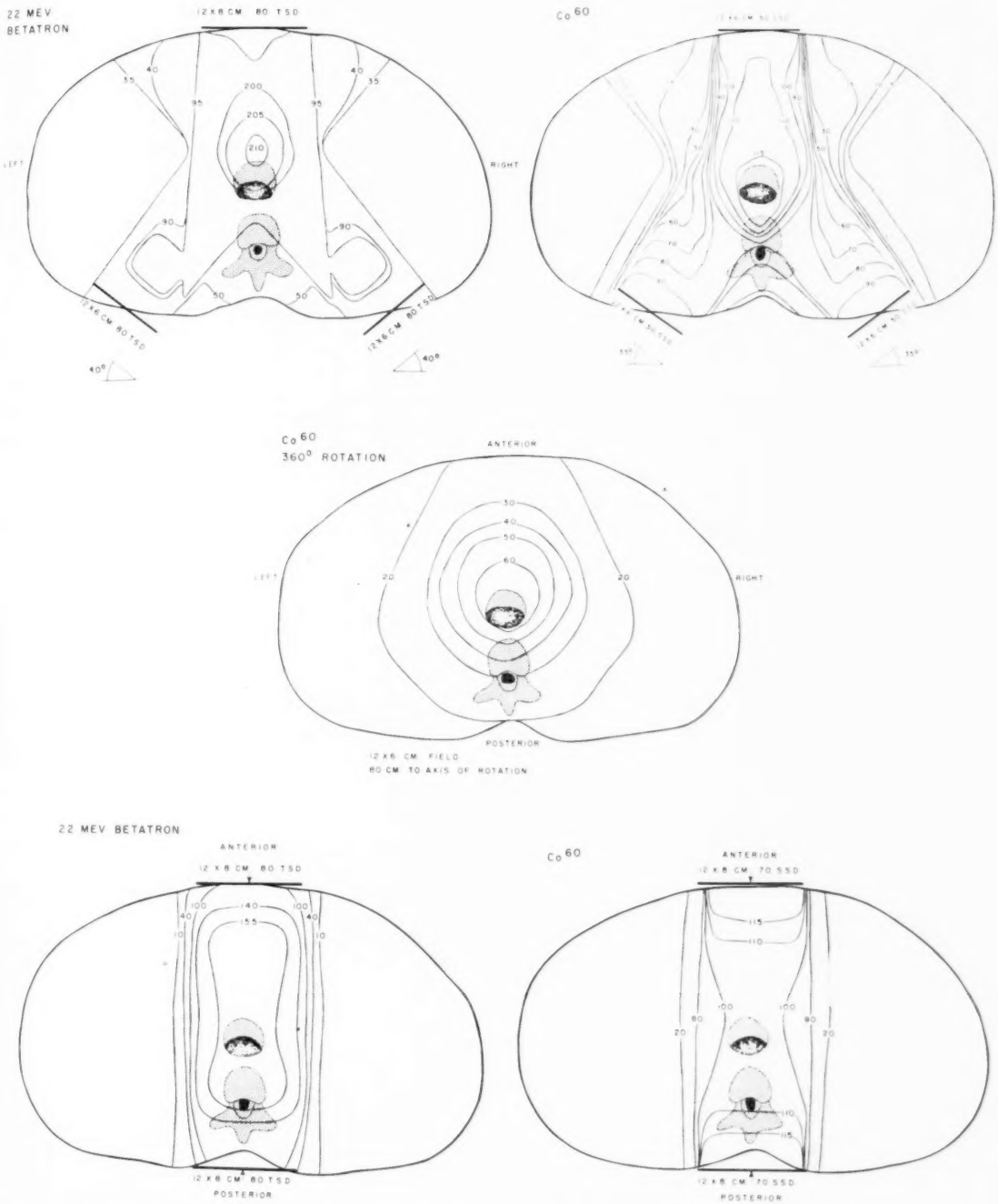


FIG. 9. The various patterns show that with the Betatron there is no subcutaneous hot spot in comparison with the Cobalt-60. A Y-shape arrangement is seemingly very satisfactory on either Cobalt-60 or Betatron but in a small number of cases it has resulted, in our experience, in excessive radiation pneumonitis, which in one instance was responsible for a quick fatal termination. Rotational pattern with the Cobalt-60 is theoretically very satisfactory. Unless fluoroscopic control is available the use of two parallel, opposing portals is anatomically the most accurate of the techniques.

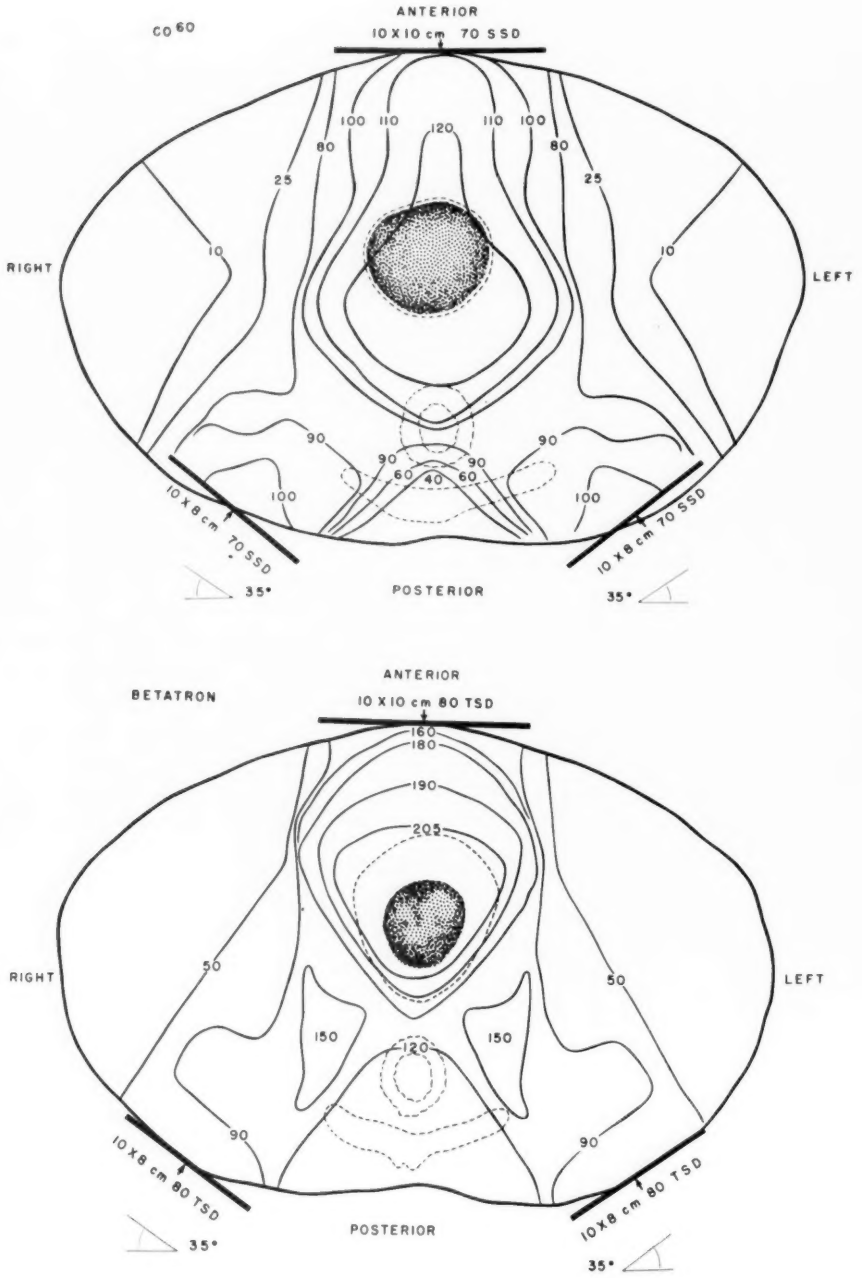


FIG. 10. (*A*) Y-shape arrangements with the Cobalt-60 unit and the Betatron for tumors of the urinary bladder. It is seen that the doses to the subcutaneous and intervening structures within the beams are more favorable with the Betatron than with the Cobalt-60. There is the possibility that the long survivors treated on the Betatron may experience less late fibrosis than those treated with the Cobalt-60.

Fig. 10. (*B*) With the Betatron the checking of the position is very satisfactory by injecting air in the bladder. It has been known that the demonstration of air-filled cavities at 1–3 mev. levels is likewise very satisfactory.

For tumors still localized to the bladder wall, relatively small fields (8 by 8 cm. anteriorly and 8 by 6 cm. posteriorly) are used, having been demonstrated to cover the whole bladder adequately and accurately. A minimal tumor dose of 6,000 r is delivered in five weeks. Only occasionally has a somwhat higher tumor dose been given. If there is paravesicular involvement larger fields (10 by 10 cm. anteriorly and 10 by 8 cm. posteriorly) are used. Should radical therapy still be indicated, a tumor dose of 5,500 r in five weeks is used. Should two parallel opposing portals be used, the same tumor dose is given in the same time. Treatments are well tolerated. A mild rectitis develops during the third and fourth weeks, usually not necessitating medication, and disappears before the end of treatment. Cystitis is not severe, in most cases subsiding in a few weeks.

All bladder cases are distributed alternately on the Betatron and the Cobalt-60 if the anteroposterior diameter is no

more than 24 cm. for the three field arrangement, and 20 cm. for two parallel opposing portals. Thicker patients are treated on the Betatron only. Because the volume distribution is more favorable with the Betatron there is less likelihood of developing late subcutaneous and connective tissue fibrosis. Rotation therapy has, so far, not been given preference due to the satisfactory anatomic coverage of the bladder and paravesicular extensions and the ease of checking the accuracy of portals.[3,5,28]

The criteria for evaluation are: (1) life span; (2) tumor regression and length of tumor control; (3) delay of appearance of extra-urinary pelvic disease; (4) bladder reactions, acute and late (irritability, ulcers, contracted bladder); (5) pelvic fibrosis; and (6) extrapelvic fibrosis.

From February 25, 1954 to June 10, 1956, 75 bladder tumor cases have had definite therapy under this program, 35 treated on Cobalt-60 and 40 on the Betatron. As observed by other authors,[2,3,5,12,27,28] supervoltage therapy is better tolerated than medium voltage therapy. Lasting control is improved and late complications are less frequent. Both Cobalt-60 teletherapy and 22 mev. Betatron are more effective tools. The tolerance to treatment is slightly but not significantly better with the Betatron. Length of follow-up and number of cases are still inadequate to draw conclusions regarding relative effectiveness and complications.

CARCINOMA OF THE UTERINE CERVIX

In Stage I and early Stage II squamous cell carcinomas of the cervix intracavitary radium therapy or transvaginal roentgen therapy, supplemented by moderate doses to the pelvic walls from external irradiation, is eminently curative. A radical attempt to sterilize, by high parametrial doses, metastatic involvement of the pelvic wall lymph nodes, which exists in a percentage of Stage I and early Stage II cases, is fraught with risks which might not be commensurate with the benefits derived. There have been indications from several centers that an increase in parametrial dosage in early stages actually lowers the cure rate.[14,22] Late Stage II, Stage III and Stage IV carcinomas of the cervix present a different situation. Increasing doses to the pelvic walls result in higher cure rates.[3,21,22] Massive disease justifies the increased risk of complications. There have been conflicting opinions on the results of supervoltage therapy in carcinomas of the cervix; some authors have failed to see any increase in cure rate,[5] whereas others, in limited and partially selected series, have produced an appreciable increase in cure rate by delivering higher doses to the lateral aspects of the parametria and pelvic walls.[1,3,19] An extensive clinical trial is therefore warranted, keeping in mind that the sterilization of squamous cell carcinomas within the pelvis still can be followed by failure due to distant metastases, which are more common than previously thought. However, long lasting palliation, manifested by several years of normal life, is still attained in those cases.

In the late stages of squamous cell carcinomas of the uterine cervix, intracavitary radium or transvaginal roentgen therapy obviously encompasses only a fraction of the disease within its lethal zone of action. The integration of intracavitary radium therapy or transvaginal roentgen therapy with external irradiation, delivering higher doses to the lateral aspects of the parametria and pelvic walls, has proven successful, but fails, in a percentage of cases to sterilize all tumor within the pelvis.

The ability to deliver high doses to the whole pelvis either with the Cobalt-60 or the Betatron warrants a reversal of the emphasis on local therapy versus external irradiation, *i.e.*, utilize whole pelvis irradiation to its maximum and then radium or transvaginal roentgen therapy as a supplement. Watson[27] has gone further and used external radiation only; a group of cases, treated with 6,000 r in three weeks, had too high an incidence of severe reactions and treatment was changed to 7,500 r in five weeks.

Classical techniques delivering seemingly

inadequate doses to the pelvic walls have unquestionably cured a percentage of patients with Stage III cancer of the cervix. This has been demonstrated by the proven cases of Kottmeier,[18] and also by the systematic percentage of cured Stage III cancers of the cervix, which can not be all inflammatory infiltrations of the parametria and pelvic walls. It was decided to deliver 4,000 r or even 6,000 r to the whole pelvis, in the late Stage II, Stage III and Stage IV cases, and reduce the radium therapy. In this way all tumor within the pelvis receives a tumor dose which should be sterilizing to a fair percentage of squamous cell carcinomas. Radium therapy is kept to avoid vault recurrences. In following this plan of treatment there is considerable regression of the tumor on the cervix with, consequently, a more effective geometry of the radioactive sources when radium therapy is performed because when there is a bulky, craterizing, or endocervical tumor, the zone of effectiveness of the intracavitary radium does not even encompass the palpable tumor.[10]

The plan of treatment was originally: (1) In the late Stage II, or Stage III cases, with possibility of good radium geometry, 4,000 r were given to the whole pelvis followed by about two-thirds of the conventional radium therapy (modified Manchester technique); (2) if the radium geometry was poor, due to old age or gross distortion of the vault, and if adequate transvaginal roentgen therapy was impossible, then 6,000 r were delivered to the whole pelvis followed by half the conventional radium therapy; (3) if after the delivery of 6,000 r in six weeks, there was still marked induration on one side, 1,000 r extra was delivered to that side; (4) if there was a frozen pelvis, whole pelvis doses of 7,000 r in seven weeks or 8,000 r in eight weeks were tried.

The aim, using either the Cobalt-60 unit or the Betatron was to give 6,000 r to the pelvic walls in six weeks. Stationary Cobalt-60 teletherapy would deliver 7,000 to 7,500 r to areas in the subcutaneous tissues and muscles (Fig. 11). The risk of late fibrosis would be excessive. Rotation therapy was used in several cases but severe small intestinal diarrheas, at times bloody, developed, using either 10 cm. or 13 cm. wide portals (Fig. 11). A maximum dose of 4,500 to 5,000 r can be given to the pelvic walls in six weeks without severe small bowel reactions. After that trial, all cases receiving 6,000 r have been treated on the Betatron.

One hundred and fifty late Stage II and Stage III cancers of the cervix have now been treated according to this program, with a minimum of nine months follow-up.

Since January, 1955, all consecutive Stage III cases have been submitted, three months following treatment, to a transperitoneal lymphadenectomy to determine the effectiveness of radiation on pelvic wall lymph nodes. In a group of of 80 such cases, the incidence of positive pelvic wall lymph nodes within the true pelvis, *i.e.*, obturator, hypogastric and external iliac lymph nodes has been about 15 per cent.

The follow-up of that group treated with high whole pelvis doses shows:

(1) If there has been previous surgery, or marked pelvic inflammatory disease, small bowel conplications are higher. Probably due to adhesions the same loops of small intestines stay in the beam. Now 5,000 r only are given in five weeks.

(2) In the cases of frozen pelvis, tumor doses of 7,000 r in seven weeks, and 8,000 r in eight weeks have not been beneficial. Small bowel necrosis has appeared which produced death. At autopsy there was no evidence of disease in several cases. Therefore, it seems that in frozen pelves radical treatments, even if sterilizing the cancer, are not justified.

(3) If at the end of 6,000 r there is still a stony hard induration of one pelvic wall, extra radiation is not warranted.

(4) If 4,000 r are delivered to the whole pelvis a maximum of 5,000 mg. hr. of radium (Manchester technique) is now the limit. If 6,000 r have been given, the limit is set at 3,000 mg. hr.

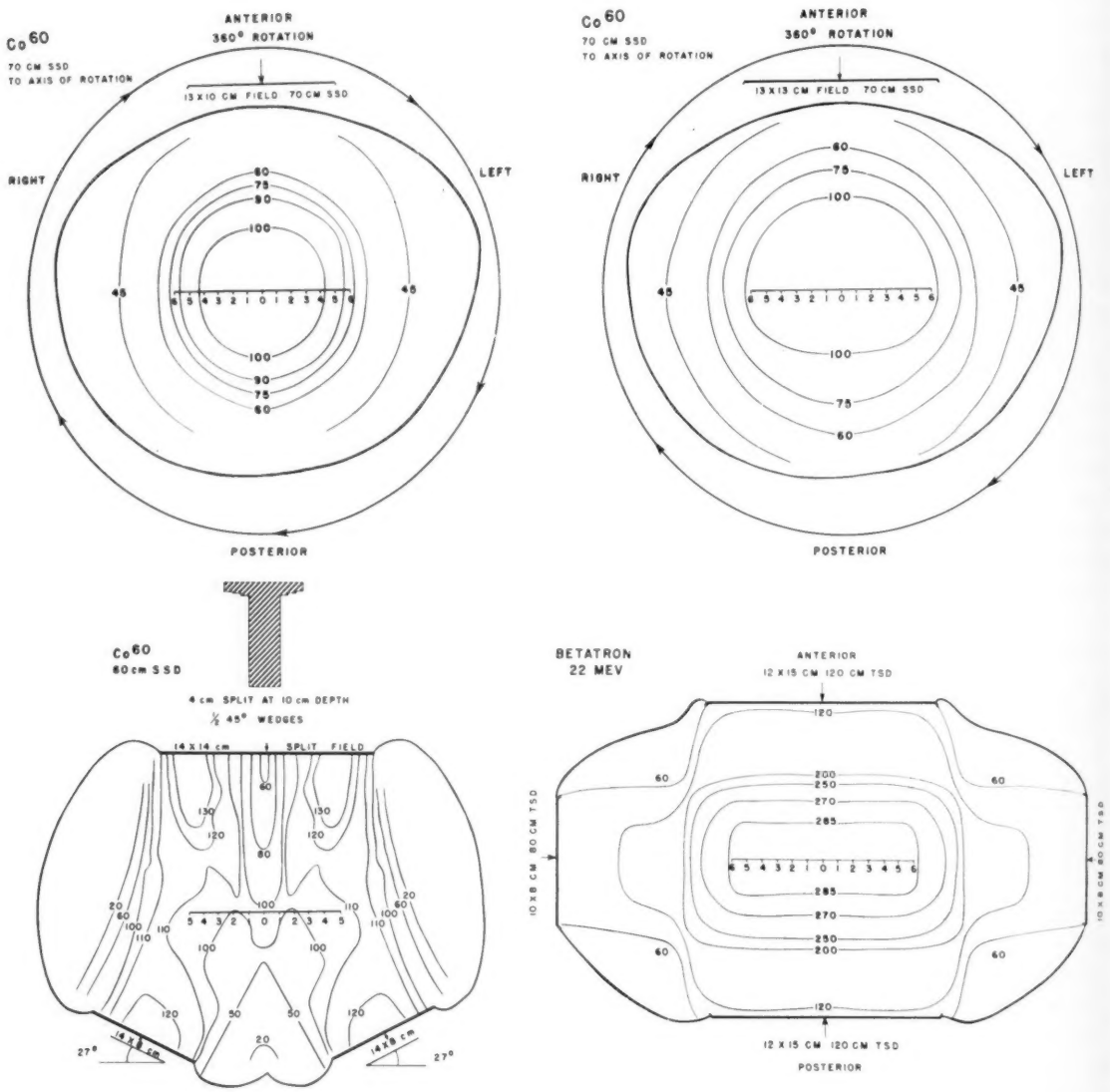


FIG. 11. Comparison of the volume distributions of the whole pelvis high dose technique with stationary portals with the Cobalt-60, stationary portals with the Betatron, and rotation technique with the Cobalt-60 brings out the following points: (1) in Cobalt-60 stationary technique there are some subcutaneous hot spots and a favorable increase in gradient of dose rate from the midline to the pelvic wall. This dovetails with intracavitary radium therapy; (2) that anterior, posterior, and lateral portals with the Betatron produce an ideal volume distribution; and (3) that using either a 10 cm. wide portal or a 13 cm. wide portal with the Cobalt-60 unit, the rotational pattern is such that if one wants to deliver 6,000 r to the pelvic wall, the more medial parts of the pelvis will receive approximately 7,000 r. Most of the slab of the body (which is 14 cm. long) is within the 45 per cent curve, *i.e.*, will receive close to 3,000 r. This large integral dose, with the inability to displace out of the true pelvis the small bowels as efficiently by strapping the patient as with compression cones, has constantly resulted in very severe diarrheas, at times bloody, developing at the end of the second or in the third week forcing the interruption of treatment. It has been found that a pelvic wall dose of 700 r per week is the maximum tolerated.

The doses at Point A and Point B are calculated but not used as a guide. The volume distribution is entirely different from classical radium therapy supplemented with external irradiation and the experience acquired does not necessarily apply. In addition, the complications have been primarily with the small bowels and sigmoid colon and the doses at Point A and Point B have no bearing on the doses received by these structures.

A short follow-up shows an appreciably larger number of survivors at one year in the Stage III group than previous to the supervoltage therapy era. Also the low incidence of positive metastatic pelvic wall lymph nodes in consecutive Stage III cases (including frozen pelves) indicates the effectiveness of the treatment. High dose whole pelvis irradiation, followed by some local irradiation, either transvaginal roentgen therapy or intracavitary radium therapy, seems to be effective. An optimal dosage must be searched for.

DISCUSSION

Clinical investigation differs from biologic experimentation in many ways. In clinical investigation the cases are limited and individual variations prevent rigid randomization, so important in biologic experimentation. Unlike biologic experiments, the variables cannot be changed at will. It is true that radiosensitivity curves have been established for small skin carcinomas but the same curves cannot be determined for squamous cell carcinomas of the mucous membranes where failure of the original treatment almost invariably results in fatality. The perusal of the literature of the last twenty years on supervoltage therapy demonstrates the difficulties confronting the clinical investigator.

The study of optimal dosage can only be made by changing either volume, dose, or time after complications or recurrences have appeared. These will require several years to be demonstrable by statistical methods even if abundant material is available.

Optimal supervoltage techniques are not medium voltage techniques transferred by using a universal RBE factor, but autonomous techniques devised and tested on their own merits by determining the optimal volume-dose-time relationships for the various clinical entities. Supervoltage therapy is fraught with certain pitfalls due to the possibilities of delivering homogeneous high doses to whole organs or whole parts of the body. This opens the possibility of replacing tested methods of interstitial or intracavitary radium therapy, alone or combined with external beam techniques, delivering extremely high doses locally. For instance, 6,000 r to the whole pelvis in six weeks are still much lower than the 30,000, 20,000 and 10,000 gamma r delivered on and around the cervix in ten days by intracavitary radium therapy. Local recurrences on one side and complication on the other side may occur with an incidence higher than in conventional methods.

An evaluation program between Cobalt-60 teletherapy units and 22 mev. Betatrons must determine the optimum volume-dose-time relationships on: (1) tumor dose; (2) mucous membrane reactions, acute and late; (3) whole organ tolerances; (4) systemic tolerance.

The clinical relative biologic effectiveness between roentgen rays of 3 mm. Cu half-value layer, Cobalt-60 and 22 mev. Betatron beam is complex. The integral dose factor cannot be completely eliminated due to side scatter and penumbra. The significance of this factor on reactions observed varies with the volume irradiated and the parts of the body. Expressing doses in roentgens (Cobalt-60 correction factor also used for Betatron calibration) the RBE is seemingly 1 between Cobalt-60 and 22 mev. Betatron for the epithelitis of the soft palate. It is 0.8 to 0.9 between roentgen rays of 3 mm. Cu half-value layer and Cobalt-60 and 22 mev. Betatron.

In the whole pelvis technique, using as test small bowel irritation (small bowel diarrhea), 600 to 700 r per week with roentgen rays of 3 mm. Cu half-value layer are as well tolerated as 1,000 r with the stationary portals technique on the Cobalt-60 unit or the Betatron, *i.e.*, an RBE of 0.65. With proper techniques, the systemic tolerance is of no concern with supervoltage therapy, and the concept of integral dose is more significant when applied to the part of the body irradiated. As the volume irradiated increases, the same number of roentgens are seemingly better tolerated with the Betatron than with the Cobalt-60 unit. If the RBE on tumor regression is the same, it is to the credit of the 22 mev. beam. If the doses are expressed in rads, the 22 mev. rad is seemingly more effective than the Cobalt-60 rad whereas for large volume irradiation the two appear more nearly equal. (See Appendix.)

Another observation is the narrow spread of individual reactions. This applies both to intensity of reactions for same doses and to degrees of intensity for different doses and times. For instance, 6,000 r in four, five, or six weeks produces, with a narrow spread, the same degrees of epithelitis (confluent, studded, red angry) in all patients.

CONCLUSION

A program of comparative evaluation of a kilocurie Cobalt-60 teletherapy unit versus a 22 mev. Betatron has been outlined with the view to determine the place of higher energy levels in the radiotherapeutic management of cancers. The details of the techniques (tumor doses, geometry, combination of external beam and gamma-ray therapy) are in trial stage and already changes have been felt necessary. The clinical correlation of dosages expressed in roentgens or rads is not yet settled.

The program presented has been designed to evaluate the clinical usefulness of a certain type of teletherapy Cobalt-60 unit versus a 22 mev. Betatron. It is not intended to demonstrate that a 22 mev. Betatron and a Cobalt-60 teletherapy unit are equivalent, as obviously this premise is erroneous. This study was undertaken to determine the usefulness of higher energy beams within the supervoltage range by the evaluation of results on those cancers treated alternately on the Cobalt-60 and 22 mev. Betatron, and to determine the percentage of those cases within the total group which would not have been treated as well without the 22 mev. Betatron.

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Appendix

DOSIMETRY AND RELATIVE BIOLOGIC EFFECTIVENESS

By W. K. SINCLAIR, Ph.D.†

IN COMPARING one radiation quantitatively with another, we aim to express the ratio between two doses producing the same biologic effect. We call this ratio the relative biologic effectiveness (RBE). The criteria that need to be satisfied in order to realize an RBE that has some meaning are, (1) that the biologic effect compared should be the same in nature and intensity, and (2) that the doses should be expressed in the same units. The difficulties of comparing effects in simple biologic systems are well known. In more complex systems the various biologic entities involved in the radiation syndrome are interwoven in such a way that it is very difficult to be certain that the same effect is in fact being measured. However, apart from the biologic problems which are well known, the second condition, namely that the dose be expressed in the same units, also presents appreciable problems which are often ignored. Many of the difficulties in dose specification are far from solved, but in the case of supervoltage radiations such as those described in this paper, experimental work has advanced to such a stage that reasonably accurate estimates can now be made if the proper units are used.

Evidently the unit to be used must express the energy absorbed in the biologic medium and presumably uniformly distributed throughout it. Consequently the rad should be used throughout. Since the

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absorbed dose will in general be derived from an ionization measurement of exposure, it is necessary to provide numerical factors by which the conversion may be made at each energy. As a result of the calculations and measurements of Laughlin and others, it is possible to do this although at 22 mev. additional experimental confirmation would be desirable.

In order to translate the data and measurements of Laughlin into practical use and to reduce errors due to varying calibration procedures in different institutions, intercomparisons were recently undertaken which enable the relationship between nominal roentgens in different institutions and rads to be established.

In the M. D. Anderson Hospital the calibration procedures for *exposure* determinations are as follows:

(1) *200 kv. and 250 kv.* 25 r, 100 r, and 250 r chambers calibrated at the National Bureau of Standards for each of the qualities involved are regularly used in air. Qualities used range from half-value layer of 1.3 mm. Cu to half-value layer of 3.4 mm. Cu.

(2) *Cobalt-60.* 25 r chambers calibrated "whole stem" at the National Bureau of Standards are used. Measurements are made in air with a 4 mm. lucite cap and the 25 r chamber used "half stem." The correction factor is modified from "full stem" to "half stem" to take account of insulator leakage. For example, a 25 r chamber having a correction factor of 1.00 at 2 mm. copper half-value layer has a "full stem" correction factor of 1.095 for Cobalt-60 (mean of two calibrations) and a "half stem" correction factor of 1.11. The 100 r and 250 r chambers sometimes used for measurement are calibrated against the 25 r, chamber, both "half stem."

(3) *Betatron 22 mev.* Measurements are made with 25 r, 100 r and 250 r chambers (100 r most frequently). The relationships between chambers are checked regularly. The chamber is mounted in the center of a 9.5 cm. cylindrical lucite block (this has been shown to be less than 1 per cent different from the 11.5 cm. square block of the National Bureau of Standards) and the beam flatness checked regularly. Up to the present the same correction factor as for Cobalt-60 radiation is used, and called nominal "*r*."

Expression of dose in rads. The tissue dose may be derived from the exposure by multiplying the nominal values of "*r*":

(1) 0.97 for 2 mm. Cu half-value layer (0.96 for 1.25 mm. Cu);
(2) 0.98 for Cobalt-60 radiation;
(3) 0.88 for Betatron 22 mev. roentgen rays.

All doses expressed in roentgens or nominal roentgens in the preceding text should be multiplied by these factors to express the dose in rads. For example, this would mean that a tumor dose of 6,000 r corresponds to:

5,800 rads at 250 kv. 2 mm. Cu half-value layer;
5,900 rads at Cobalt-60;
5,300 rads at 22 mev. Betatron.

Modifications should also be made to the estimate of the clinical RBE expressed in roentgens after expressing both tissue doses in rads.

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SOME OBSERVATIONS ON THE CLINICAL EFFECTS OF COBALT-60 TELECURIE THERAPY*

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FOR the past four years a Cobalt-60 telecurie therapy apparatus has been in use at the Saskatoon Cancer Clinic.[2,3,5] It has been used routinely for treating those patients who would previously have been treated by 400 kv. roentgen rays. Not only has the apparatus proved simple to operate, but it has enabled us to attain higher tumor doses in some instances, and it has made possible the radical treatment of certain tumors which previously would have only been treated palliatively. We are not yet prepared to compare survival figures with those previously attained, but we have made certain clinical observations which will be discussed in this paper.

TUMOR DOSES ACHIEVED

Doses in air and on the surface of the skin are an inadequate way of expressing dosage, especially with the Co^{60} telecurie apparatus. It is only the tumor dose (or tissue dose) which gives an accurate indication of what is likely to be achieved. Consequently, all our doses are expressed as so many roentgens at the tumor, given over a certain period of time. Most patients have been treated with either 15 or 25 daily exposures being given over a three or five week period. Actual tumor doses will be stated when individual sites are discussed; however, as a rule, it has been possible to deliver a tumor dose 10 per cent higher than that with conventional radiation.

REACTIONS

The reactions of the irradiated tissues are much as one would expect on theoretical grounds. These reactions are often different from those obtained by the use of conventional radiation either because of the inherent quality of the radiation or because it has been possible to use a treatment plan which has reduced or eliminated a previously observed reaction.

Skin reactions have been much less than with conventional roentgen radiation. This is due to the fact that the maximum dose of a given beam occurs at some 4 mm. below the surface of the skin. We devised an experiment using graduated thicknesses of lucite over the applicator end, whereby the 100 per cent dose level could be varied from 3 mm. below the skin surface to 2 mm., 1 mm., and 0.5 mm.[1] The skin showed graduated degrees of erythema with the most pronounced reaction under the 3 mm. thickness of lucite. This result corresponded to the actual surface dose measured under each section. These experiments demonstrated the skin sparing effect of Co^{60} telecurie therapy, allowing the administration of larger tumor doses even with large fields, and making it possible to use more simple set-ups in treating deep-seated tumors. On the other hand, in order to utilize this skin sparing effect to the greatest advantage, the applicator ends must not be covered nor should bolus material, wax or plaster be used between the applicator end and the skin through which the rays must pass. This has made it necessary for us to employ new treatment techniques in many areas. These will be mentioned when particular sites are discussed.

It will be impossible to discuss every type of case which has been treated by means of the Co^{60} unit. Suffice it to say that nearly every type of cancer has been treated, even though, in some instances, only 1 or 2 cases were tried. There is nothing inherently different in Cobalt radiation that will make a radioresistant

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cancer curable. Consequently, our use of the apparatus has been largely confined to treating those patients who have radiocurable cancers, preferably deep-seated in their location.

CANCER OF THE BREAST

Our policy with regard to postoperative cancer of the breast is to irradiate the axillary and supraclavicular areas of the involved side only if metastatic lymph nodes are discovered at radical mastectomy. In addition, if the lesion is located in the inner half of the breast, the parasternal area is irradiated even though no axillary lymph node involvement is found.

The radiation technique consists of using parallel opposing fields 20 by 10 cm. in size (or less), the lower edge of which runs horizontally across the chest 6 cm. below the mid-point of the sternal notch. This technique was chosen so that a 15 by 6 cm. parasternal field could be added without there being a "gap" or overlap between the fields.

When we first started to use the Co^{60} unit, we gave a dose of 4,400 r to the central part of the axilla and a skin dose of 4,950 r to the parasternal area over a three week period. The skin doses to the axillary area varied from patient to patient in the range of 4,500 r 5,200 r. These doses, it must be remembered, are the maximum doses which occur 3 to 4 mm. below the surface. The actual surface dose varied from 2,500 r to 3,000 r. This is the "average" dose calculated at the center of the field. Since the treated area is thinner in the supraclavicular than in the infraclavicular fossa and since no bolus is used, this surface dose varies over the treated area but probably never exceeds 4,000 r. The thinness of the supraclavicular part of the area is probably compensated for by the greater amount of lung tissue in the path of the beam through the infraclavicular fossa. The skin, in any case, seldom showed more than a moderate erythema, even though this high central dose was attained.

A rather frequent complication, however, did occur in the form of radiation changes in the apical part of the lung. A radiograph (Fig. 1), taken at the time of treatment, shows that a fairly large part of the lung is in the radiation zone and this probably accounts for the large number of patients who developed changes. In some cases there were no symptoms, even though roentgen examination of the chest showed radiation changes. In other patients there were rather severe symptoms in the form of an irritative cough, dyspnea, and fever. The

FIG. 1. Radiograph taken during Co^{60} postoperative irradiation of the axillary and supraclavicular areas in a case of carcinoma of the breast.

symptoms were always worse if the patient had received parasternal as well as axillary and supraclavicular radiation. The lung changes are always, at first, in the form of a radiation pneumonitis which may clear completely or persist and lead to pulmonary fibrosis. Some patients also seem to develop an atelectasis of the involved pulmonary segment. Of 74 consecutive patients who had been treated by this technique, 46 per cent developed some type of radiation change. However, of these, only 18 per cent had symptoms which could be attributed to the radiation; 23 per cent, who did develop changes, showed complete clearing during the time under observation. Figures 2, *A*, *B* and *C*, 3, *A*, *B* and *C* and 4, *A*, *B*, *C* and *D* demonstrate these changes and Table 1 shows the pulmonary findings with different doses. As a result of this experience, we now give a central tumor dose of 4,200 r to the axilla and a dose of 4,200 r to the parasternal area.

INTRINSIC CARCINOMA OF THE LARYNX

In treating carcinoma of the larynx, various techniques have been employed. At first we constructed plaster casts for the head and neck and used a 3 field beam-directed technique. This involved the use of wax build-ups for the location of the various fields so that both plaster and wax were interposed between the applicator end and the skin. We were, therefore, not utilizing the skin sparing effect of Co^{60} radiation. Furthermore, a certain degree of care had to be exercised in this set-up so that the spinal cord should not be in a high dose zone. Hence, this technique was abandoned in favor of a parallel-opposing pair of fields directed from side to side. This technique resulted in a homogeneous dose throughout the irradiated part of the neck, and, although it produced an adequate distribution of radiation to the larynx, it raised the dose on the surrounding tissues to a high level as well, with consequent severe immediate reaction to all the tissues concerned. From this expereience we have devised our present method of treating intrinsic carcinoma of the larynx. We now use a pair of fields at right angles to each other. These fields have a "wedge" filter so that the thick part of the wedge is near the apex of the 90°. Figure 5 illustrates the satisfactory distribution of radiation obtained from such a set up. A jig is used to

TABLE I

PULMONARY CHANGES IN 74 CONSECUTIVE PATIENTS WHO RECEIVED POSTOPERATIVE Co^{60} THERAPY TO THE AXILLA AND/OR PARASTERNAL AREAS

Technique	Dose	No. of Patients	No. Showing Post Radiation Pulmonary Changes	No. Which Subsequently Cleared
Co^{60} Axilla only	4125 r	18	7	3
Co^{60} Axilla only	4400 r	23	11	2
Co^{60} Axilla and Parasternal	4125 r 4400 r	7	4	1
Co^{60} Axilla and Parasternal	4400 r 4400 r	4	1	0
Co^{60} Axilla and Parasternal	4400 r 4950 r	18	11	2
Co^{60} Parasternal only	4400 r	4	0	0
	Total	74	34	8
	Percentage	100	46	23

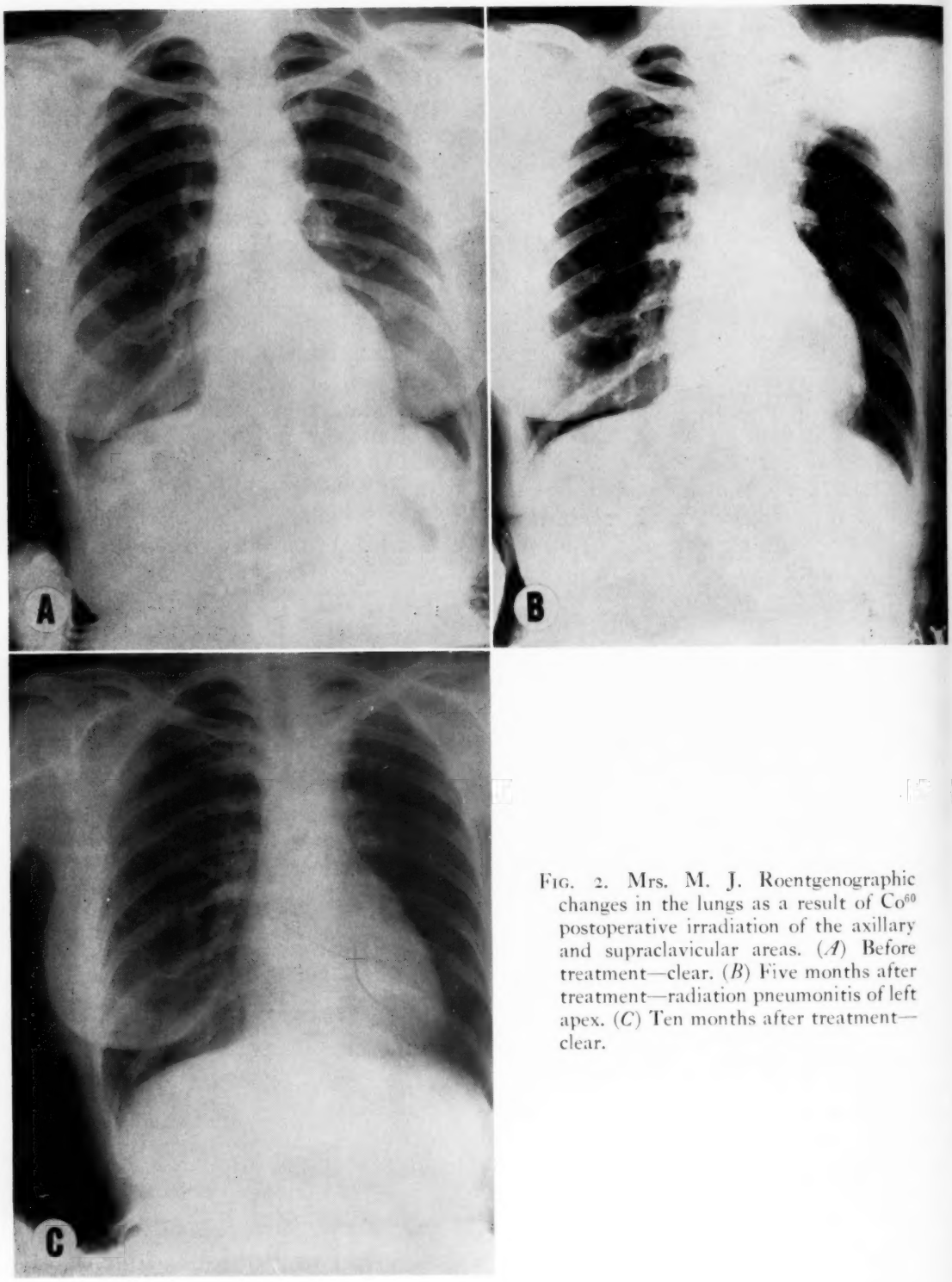

FIG. 2. Mrs. M. J. Roentgenographic changes in the lungs as a result of Co^{60} postoperative irradiation of the axillary and supraclavicular areas. (*A*) Before treatment—clear. (*B*) Five months after treatment—radiation pneumonitis of left apex. (*C*) Ten months after treatment—clear.

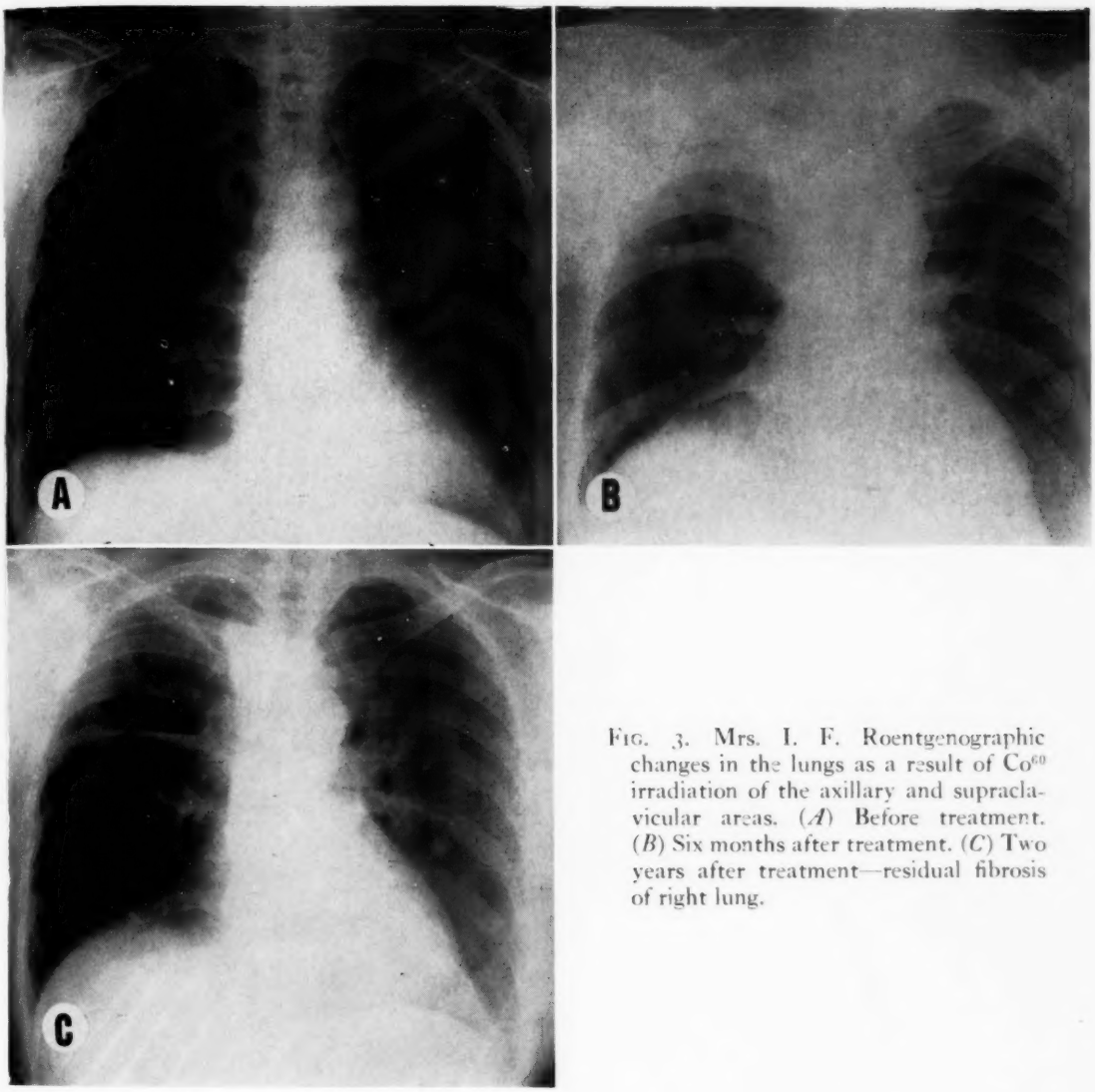

FIG. 3. Mrs. I. F. Roentgenographic changes in the lungs as a result of Co^{60} irradiation of the axillary and supraclavicular areas. (*A*) Before treatment. (*B*) Six months after treatment. (*C*) Two years after treatment—residual fibrosis of right lung.

direct the beams at the correct angles, but no absorbing material is interposed between the beam and the skin so that we still have the skin sparing effect of the radiation. The fields are usually 7 by 5 or 5 by 5 cm. in size.

At first we felt that we would be able to administer considerably more radiation to the laryngeal cartilages with Co^{60} than with conventional radiation. This assumption led to unfortunate results in 3 patients who developed high dose effects in the form of gross edema of the laryngeal structures with perichondritis requiring tracheotomy. This occurred within a few weeks of treatment in 1 case and within six months in the other two. One of the patients was treated with 10 by 6 cm. fields as he had subglottic extension. The others were irradiated with small fields, either 7 by 5 or 5 by 5 cm. in size. All these patients died. Postmortem examination was performed on 2 and the high dose effect was confirmed. This resulted in a change of our dose schedule so that we now give a tumor dose of 6,000 r in five weeks. We changed from a dose of 5,450 r in three weeks to the five week plan for we felt that the immediate local reaction in the form of dysphagia and soreness of the throat was less with the longer over-all

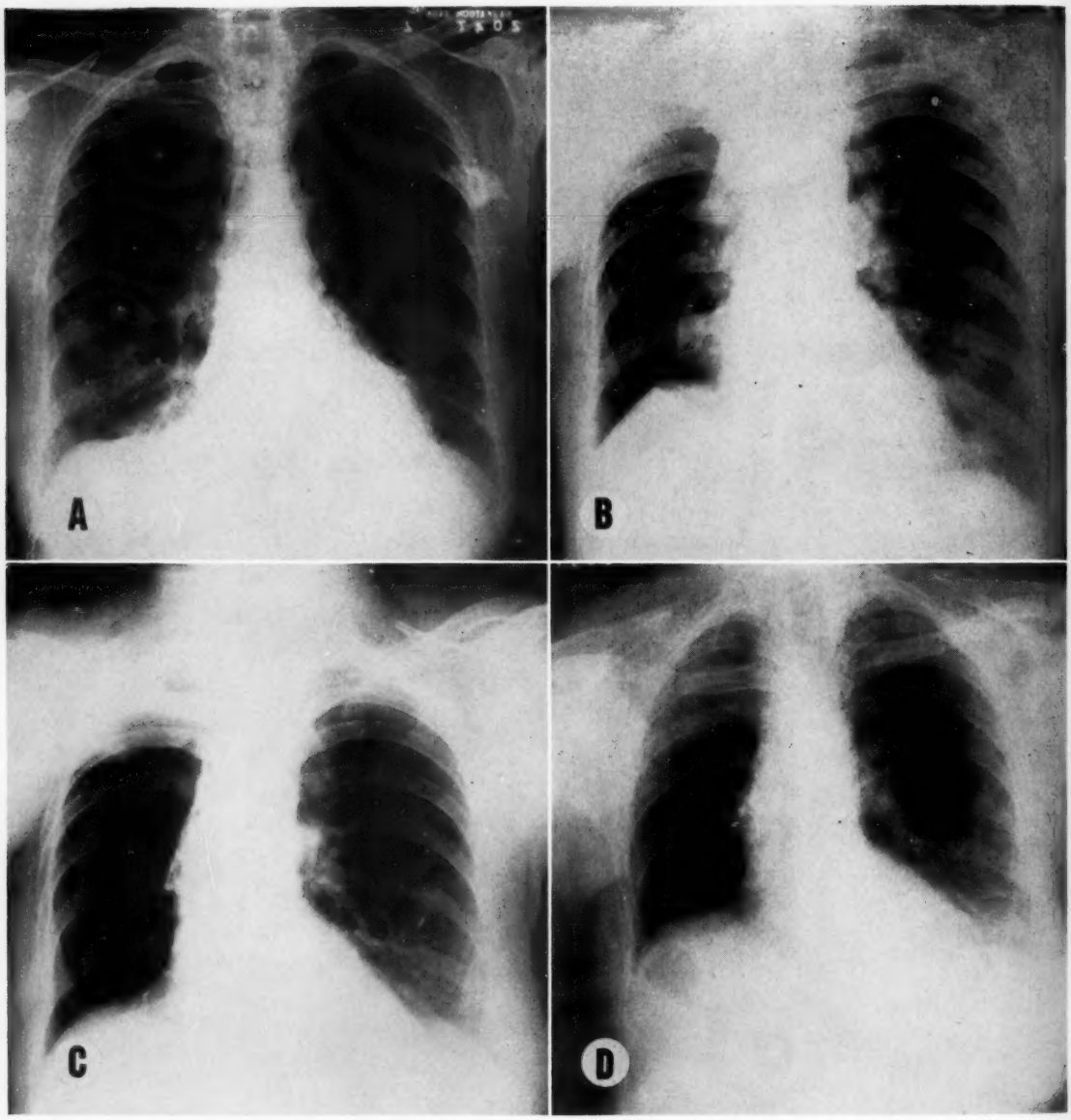

FIG. 4. Mrs. L. F. Roentgenographic changes in the right lung as a result of Co^{60} irradiation of the axillary, supraclavicular and parasternal areas. (*A*) Before treatment. (*B*) Five months after treatment. (*C*) One year and nine months after treatment. (*D*) Three years after treatment—essentially clear.

time. Figure 6 shows the results obtained with different doses given over different periods of time.

EXTRINSIC CARCINOMA OF THE LARYNX

There have been 8 patients with extrinsic carcinoma of the larynx. Several of these had metastatically involved lymph nodes when first seen. Those who had local disease only were most often treated by means of small fields, the beam being directed, in some way, toward the tumor. Most of those with metastatic lymph nodes were treated by a pair of parallel-opposing fields, often 10 by 10 or 15 by 10 cm. in size. Tumor doses as high as 5,450 r in three weeks or 6,000 r in five weeks were achieved in some cases, even though this meant a maximum skin dose of 6,100 r in five weeks in 1 patient. This produced a

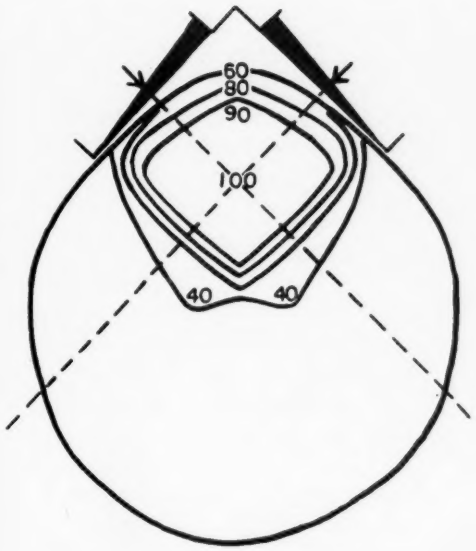

FIG. 5. Isodose distribution obtained in treating cancer of the larynx with two 5×5 cm. fields (wedge filters) at 90° to one another.

fairly marked erythema with a few areas of moist epithelitis. The mucosal reactions, however, were very severe, often making it difficult to maintain adequate nourishment during the last week of treatment and for the subsequent two to three weeks. The results, on the whole, have been disappointing. Only 3 out of 8 patients are still alive. One of these has residual disease but has lived three years. The other 2 are well at one year and three years, respectively.

CARCINOMA OF THE MAXILLARY ANTRUM

When we have a patient with an early carcinoma of the maxillary antrum, we prefer to treat that patient by means of a central radium source in the antrum. Many patients, however, are not seen until the disease is more advanced, with destruction of two or more walls of the antrum. Such patients have been treated by means of the Co^{60} telecurie apparatus. A pair of fields large enough to cover the entire involved area is used. One is directed from the front of the face so that the medial edge is on the opposite side of the midline. The second field is directed from the side of the face. These fields are at right angles to one another, and in the path of each beam is

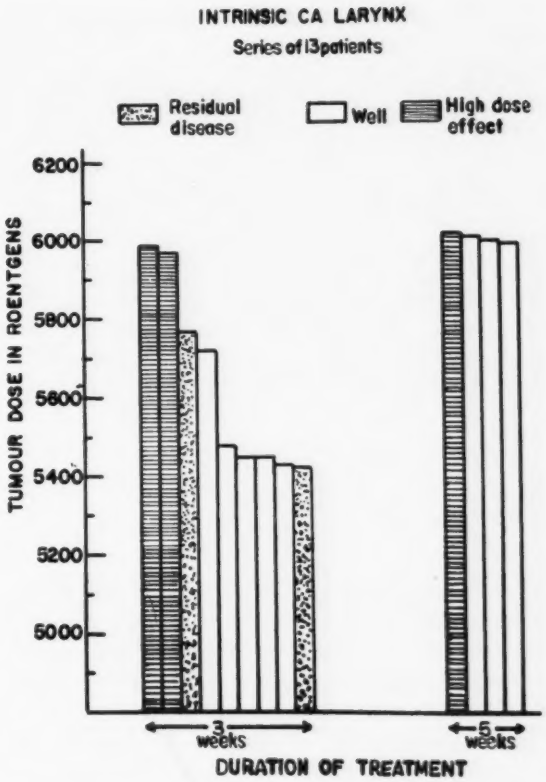

FIG. 6. Results obtained in Co^{60} irradiation for carcinoma of the larynx when different doses were given over different periods of time.

inserted a "wedge" filter. Figure 7 shows the type of isodose curves when wedge filters are used. When two such fields are combined, we obtain a distribution of radiation throughout the antrum and surround-

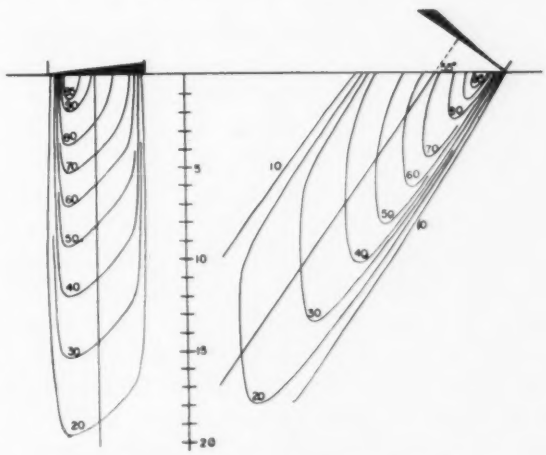

FIG. 7. Isodose curves obtained with Co^{60} using a wedge filter. No air gap.

FIG. 8. Isodose distribution obtained when two fields, using wedge filters, are used in treating carcinoma of the antrum. The fields are 90° to one another.

ing structures as shown in Figure 8. If necessary, the eye is included in the radiation field. A tissue dose of 6,000 r in five weeks is attained with only the production of a moderate skin reaction and, because of the field arrangement, only a limited amount of oral mucosa is in the high dose zone so that the mucosal reactions, although severe, are never a serious problem.

CARCINOMA OF THE CERVIX UTERI

In treating carcinoma of the cervix uteri, we use the Manchester radium technique to give 7,000 r to Point A. This gives between 2,000 and 2,500 r to Point B. In order to give Point B a possible tumor lethal dose with 250 kv. radiation, we found it necessary to use a complicated 8 field technique (4 fields on either side). Even then it was possible to give only 2,250 r in three weeks to Point B as there was enough direct and scattered radiation to induce troublesome diarrhea. With the Co^{60} unit it has been possible to give 3,250 r to Point B with a much simpler set-up which practically eliminates the radiation to the rectum. This is done by using a "split" 12 by 10 cm. parallel-opposing pair of fields applied directly anteriorly and posteriorly. The split is accomplished by inserting a block of lead 4 cm. in thickness in the base of the applicator. This block of lead is rectangular in shape, 4 by 10 cm. in size. Essentially we have a pair of 4 by 10 cm. fields on either side directed toward Point B. The isodose distribution in the pelvis when such radiation is combined with the radium is more advantageous than the distribution obtained with 250 kv. radiation. The skin, of course, shows at the most only a mild erythema.

SUPERFICIAL CARCINOMATA

Since there is less absorption of high energy radiation by bone and cartilage, this type of radiation should produce less risk of cartilage or bone necrosis. Consequently, we have used the Co^{60} telecurie apparatus for treating some skin carcinomata—where they were located over or were involving cartilage. Some examples of these were squamous cell carcinomata involving the ear or nose, and extensive basal cell cancers involving both upper and lower eyelids. In these cases, in order to give the surface of the skin the 100 per cent dose, it was necessary either to cover the end of the applicator with 3 mm. of lucite or to interpose unit density material between the applicator end and the skin. In all cases, since the size of the field used was relatively small (usually 4 by 4 or 5 by 5 cm.), a surface dose of 6,000 r was given in an over-all time of three weeks. This dose usually produced a moist reaction which rapidly cleared. There was complete regression of the tumor in all cases and, to date, there has been no recurrence. Of greater importance, however, is the fact that in no case have we encountered cartilage necrosis attributable to the radiation.

CANCER OF THE BLADDER

Twenty-one cases of cancer of the bladder have been treated with the Co^{60} unit. These were advanced cases in which the only other possible form of treatment

that could be considered would have been total cystectomy. Of these cases 13 are alive (3 with residual tumor) and 8 are dead. Of the 8 that are dead, 2 were found at postmortem to have had no residual bladder tumor and 2 other patients died from intercurrent disease. The longest survival is two and one-half years. All of these patients, except 2, were treated by horizontal rotation. The size of the field at the level of the tumor varied from 8.4 cm. square to 9.6 cm. square. The tumor doses given were high and varied from 7,200 r in thirty-eight days to 5,500 r in nineteen days. Four patients developed no constitutional or local reaction. In 11 cases there was an increase in urinary frequency and 7 cases developed diarrhea towards the end of their treatment. In every case the diarrhea subsided within two or three weeks of completing the treatment. Since rotational therapy was used, skin reactions were either absent or consisted only of a mild erythema.

CANCER OF THE LUNG

Some inoperable cases of carcinoma of the lung have been treated, provided no distant metastases were present. Twenty-three of these cases have been studied. Either rotational or large field therapy has been used, depending upon the size and site of the tumor. Tumor doses given varied from 4,000 r in seventeen days to 5,500 r in thirty-five days when large fields (*e.g.*, 2 or 3 fields of 15 by 10 to 15 by 15 cm.) were used and from 5,000 r in twenty-five days to 6,500 r in thirty-two days when smaller fields (usually 9.6 cm. square at the tumor) were used. No reaction developed in 8 of these patients. Nine cases suffered from dysphagia due to inclusion of the esophagus in the irradiated area. In only 7 cases was any erythema of the skin reported. Three patients suffered from radiation sickness or nausea. Eighteen exhibited either subjective or objective improvement or both, and in only 5 was no beneficial effect observed. Fifteen are dead and 8 are alive at the present time, the longest survival being two and one-half years. Most of these patients had an injection of nitrogen mustard immediately prior to starting their treatment, and we consider that this drug exerts a synergistic action with radiation in the treatment of this disease. We look upon this treatment as palliative and think it is well worthwhile.

Palliative treatment of secondary deposits in bone, (*e.g.*, cancer of the breast) can be carried out effectively with the Cobalt unit. Skin reactions are at a minimum and usually a single exposure is satisfactory. For secondary deposits in the spine either two fields with wedge filters can be used, or if only one vertebra is involved, horizontal rotational therapy is used, again with a wedge filter and the beam directed from the back of the patient only. High energy radiations are much more effective in the treatment of bone secondaries than are low energy radiations. Although inorganic bone absorbs far more of the low energy rays than of the high energy rays, a soft tissue mass will receive a higher dose from the higher energy rays since the shielding effect of the overlying bone is minimized and a roughly equivalent dose is delivered to the bone itself and tumor. With low energy rays, there is intense ionization in bone itself but the secondary electrons only penetrate a few microns of the tumor tissue adjacent to the bone; hence, the main mass of tumor does not benefit at all from the increased ionization produced by the bone.[4]

The lesser screening effect of bone when these high energy rays are employed is particularly useful in the treatment of tumors which are surrounded or masked by bone. A higher tumor dose through the bone can be attained. Examples of such tumors are malignant growths in the nasopharynx, which particularly tend to invade the base of the skull, and pituitary tumors, which are surrounded by bone.

CONCLUSION

Clinical experience has shown that Co^{60} telecurie therapy is a useful adjunct to the

practice of radiotherapy. There has been less trouble with skin reactions; field selection and treatment plans have been simpler; and, in many cases, it has been possible to achieve higher tumor doses than with conventional roentgen rays. As a rule, tumor doses have been approximately 10 per cent higher than those with conventional radiation in order to produce the same result. Doses higher than this have led to complications, such as cartilage necrosis, or when the lung was in the radiation path, pulmonary fibrosis.

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CLINICAL ASPECTS OF BETATRON IRRADIATION*

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ALL of the high energy radiation producing machines offer fairly common treatment advantages, and relatively minor variations in disadvantages related to methods of beam production, costs of initial equipment, operation and maintenance. After a little more than six years of experience with the 23 mev. Betatron we feel quite certain about indications for and limitations of this form of treatment. Unfortunately we still have no final conclusions about optimal dosage. It is difficult to determine the best time-dose relationship without an adequate number of similar and suitable cases since there are so many patient, normal tissue, and tumor tissue variables. This optimal dosage situation is the most important single factor holding up our final evaluation of megavoltage therapy. Very likely if more were known about time-dose relationships in clinical low voltage therapy, the solution of the problem would be considerably simplified.

Since patients tolerate very high energy radiations better from the standpoint of superficial reactions and general systemic manifestations, there is a chance to treat them more rapidly and with higher tumor doses than one ordinarily does with lower energy radiations.[2] We now know that these are advantages limited to the majority of our patients with such advanced stages of their disease that the time saving factor is the difference between complete and incomplete treatment before death. In the academic world this is important, but in the patient's practical existence more rapid treatment can become a liability. In our early experience we saw patients dying of their extensive disease before treatment was completed and autopsies would show some evidence of residual tumor. We were soon faced with the fact that the Betatron therapy rather than incomplete dosage was being blamed for some failures. As soon as we concentrated on complete dosage before death, a change occurred in autopsy findings to the extent that it became quite routine for pathologists to demonstrate to us that we had completely destroyed the primary irradiated tumor. Naturally this led to an influx of patients to be "cured" but we continued to be skeptical because we recognized the reasons why so many of these "cured" patients were dying. Most often it was simply a matter of too widespread cancer for us to adequately treat all of it. It is true that a few of our earlier patients won the gamble and lived for several years beyond what one would ordinarily predict for their type and extent of neoplasm. Some of them have developed complications from treatment, and they have contributed significantly to a modification even of our more recent techniques which we had believed to be good. In essence the problem has become twofold, first, the over-all treatment time has been lengthened, and, second, the total dose given has been lowered. It is therefore obvious that our earlier techniques involved too short a treatment period and too large a total dose to be compatible with the fewest possible late complications from management of the patient's disease. The newer techniques will reduce the extent to which we can damage some of the less radiosensitive neoplasms. We can actually see the need for a double standard in treatment planning dependent upon the radiosensitivity of the tumor and the predictable chances of a prolonged patient survival. There are some patients in whom intensive therapy will result in more positive palliation from the primary disease than distress from later complica-

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tions of the treatment. This raises the question as to whether cancer in its terminal stages causes more suffering than late radiation effects. With continued interest in this problem, we are convinced that evidence will continue to mount in favor of destroying the tumor if at all reasonably possible.

Regardless of the modality of treatment being investigated by any of the megavoltage therapy workers, apparently they all agree that relative radiosensitivity of a given tumor and one's ability to include all of the known tumor within the most intensively irradiated zone are the primary considerations in patient assignment for any form of Betatron treatment. Using very high energy roentgen-ray beams, deep seated lesions in the body are most appropriately reached. The advantages of one form of treatment over another are largely limited to the spatial depth dose distribution. Such advantages as diminished skin effect, decreased systemic radiation effects, and lessened difference between bone and soft tissue radiation absorption are all secondary and, with the exception of bone versus soft tissue absorption, are actually due to spatial depth dose distribution of the primary beam and its scattered radiations.

The distribution of our cases subjected to Betatron roentgen therapy is shown in Table I. Obviously no one group of cases is sufficiently large to analyze statistically, and a very high percentage of our patients come to us in a far advanced stage of their disease.

We feel that the chief advantages of very high energy roentgen-ray beams are slightly different in the three groups of cases listed, and that they are primarily related to: (1) Higher tumor dose in the A group of deep seated lesions; (2) less damage to healthy tissues with delivery of identical doses in the B group of less deeply seated lesions; and (3) ability to deliver a more uniform dose to a fairly large segment of the body when there are widespread or generalized metastases.

TABLE I

A. Deep Seated Lesions		
Lungs		
Bronchogenic carcinoma		
Pancoast type	9	
others	38	
solitary metastasis	1	
fibromyxosarcoma	1	
Hodgkin's disease, localized	1	
lymphosarcoma, localized	1	
		51
Esophagus		
Carcinoma		
cervical	7	
upper thoracic	4	
mid-thoracic	3	
lower thoracic	4	
		18
Digestive organs		
pancreas carcinoma	1	
Hodgkin's disease of cecum	1	
rectal carcinoma	1	
		3
Genitourinary organs		
bladder carcinoma	3	
uterine body carcinoma	2	
uterine cervix carcinoma	6	
		11
Total		83
B. Less Deep Seated Lesions		
Brain		
glioblastoma multiforme	9	
astrocytoma	2	
oligodendroglioma	1	
ependymoma	2	
hemangio-endothelioma	1	
papillary adenocarcinoma	1	
cerebellar sarcoma	2	
chordoma ? (not verified)	1	
acoustic neurinoma	1	
pituitary adenoma	4	
chromophobe	2	
eosinophil	2	
pituitary carcinoma	1	
craniopharyngioma	2	
experimental (generalized carcinoma)	2	
		29

TABLE I (*continued*)

Spine		
glioblastoma multiforme	1	
astrocytoma	2	
neurogenic sarcoma	1	
multiple myeloma	1	
giant cell tumor	1	
		6
Nasopharynx		
lymphosarcoma	1	
		1
Oropharynx		
alveolar ridge carcinoma	1	
soft palate carcinoma	1	
tongue carcinoma	7	
extensive carcinoma	5	
tonsillar Hodgkin's disease	1	
		15
Larynx		
intrinsic carcinoma	3	
extrinsic carcinoma	5	
		8
Total		59
C. Spray Radiation (advanced diseases)		
Extensive lesions	5	
Disseminated metastases	20	
Generalized diseases	13	
Total		38
Grand Total		180

The first group of patients to be discussed is *the deep seated A group* where Betatron therapy is preferred because of our ability to deliver a higher depth dose.

Our lung tumor patients include 9 with Pancoast type of tumor. The survival of these 9 patients is as follows: 4 years—1, died probably without tumor; 2 years, 9 months—1, died probably without tumor; 2 years, 4 months—1, living and working, no evidence of disease; 1 year, 5 months—1, died of other cause and probably without tumor; died of cerebral metastases—1, autopsy showed no residual neoplasm on serial sections of primary tumor area; died after insignificant palliation with extension of tumor to the spine and cord—2, both showed recalcification of previously destroyed ribs in their post-treatment period; died recently—2.

In another group of 3 patients the tumor mass presented in the upper mediastinum with little evidence of bronchopulmonary alteration. One person died of liver and general abdominal metastases. He had complete relief of vena cava syndrome and regression of the mediastinal lesion. Another had a year symptom free and useful life. He died of perforated trachea, but no residual tumor could be found at autopsy. The third lived ten months seemingly without recurrence. He died of postoperative hemorrhage after repair of a gastric ulcer perforation (Fig. 1).

The largest group of lung cases were far advanced carcinomas and had known metastases, extensions to the carina, attachment or invasion of vena cava, aorta, or pericardium, and wide pleural dissemination. The response in this group to treatment, it seems, is predetermined and incalculable. Some patients in relatively good condition and in a less advanced stage of the disease die in a short time uninfluenced by treatment. Other very advanced cases respond surprisingly well. For example, one patient, still living two years after treatment and without evidence of tumor, seemed to be in a preterminal stage with extensive involvement of the upper and middle lobes and the mediastinum, and had several ribs destroyed by the carcinoma. Four other advanced cases survived a year. As a result of these experiences, there are relatively few patients we approach with palliative intention. Chest physicians, who also see these patients in follow-up sessions, have indirectly offered a strongly favorable opinion as to the effectiveness of the treatment (Fig. 2).

We have had similar experiences in treating esophageal cancer. Of the 18 cases treated, 7 had cervical, 4 upper thoracic, 3 mid-thoracic, and 4 lower thoracic lesions.

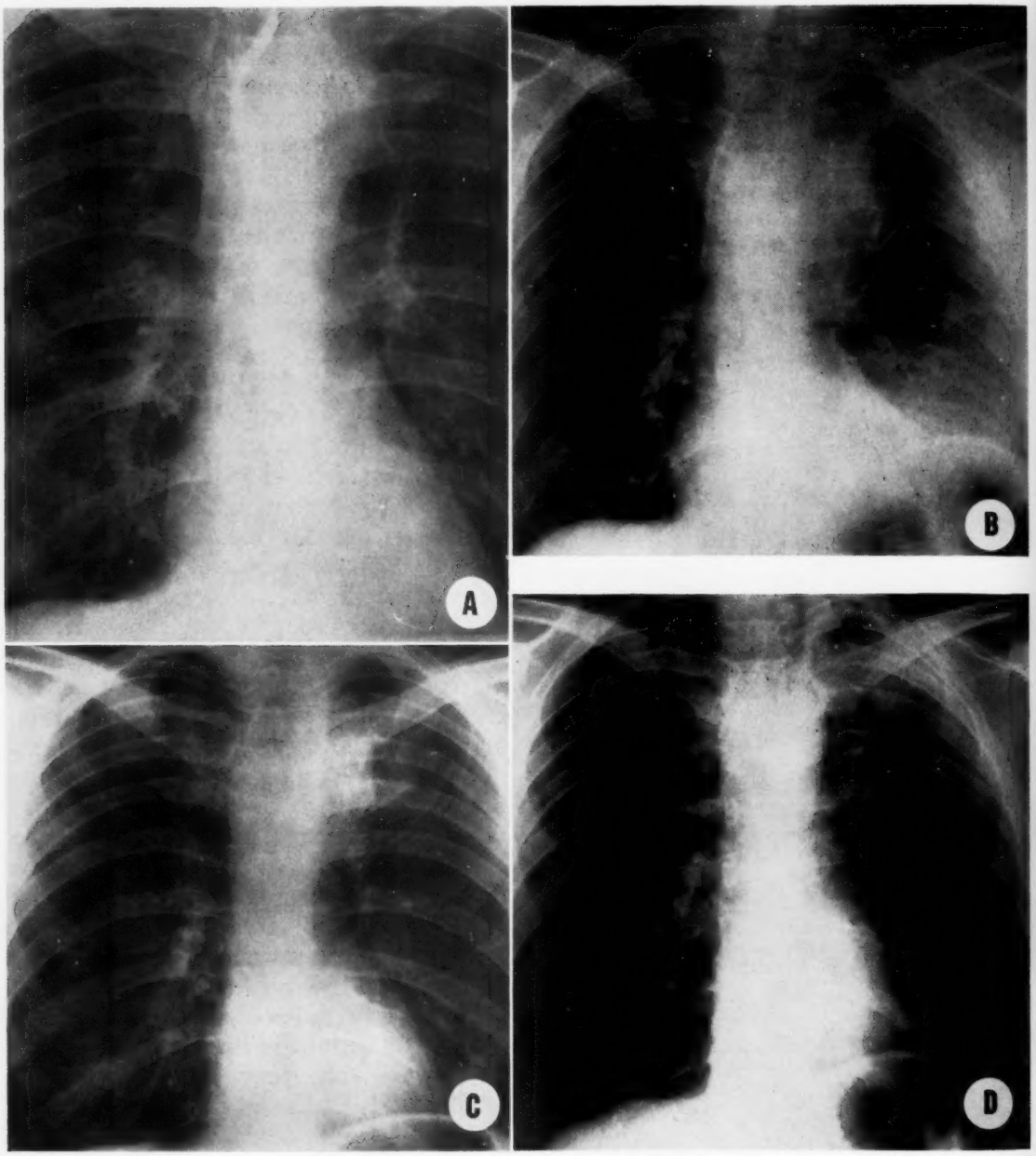

Fig. 1. Forty-one year old white male. Heavy smoker and drinker. Hoarseness, chest pains, dysphagia, loss of 20 pounds, and disability for 3 months before irradiation. (*A*) September 2, 1953. Tumor mass in upper mediastinum shifting the trachea and esophagus moderately to right and extending into the left lung field. (*B*) October 8, 1953. After exploratory thoracotomy: increased tumor mass—paralyzed left diaphragm. (*C*) November 18, 1953. Near completion of Betatron therapy: marked regression of tumor. (*D*) Ten months after completion of treatment: tumor shadow disappeared—no clinical evidence of residual tumor. (Died of acute hemorrhage after repair of perforated gastric ulcer.)

Nearly all of them were in a far advanced stage of their disease. The few less advanced cases were referred to us because coexistent heart diasese or suspected metastases, etc., contraindicated the type of surgery which would have had to be performed. We have seen metastases develop before, during, and after treatment. Some of these patients died of acute hemorrhage possibly related to destruction of the tumor

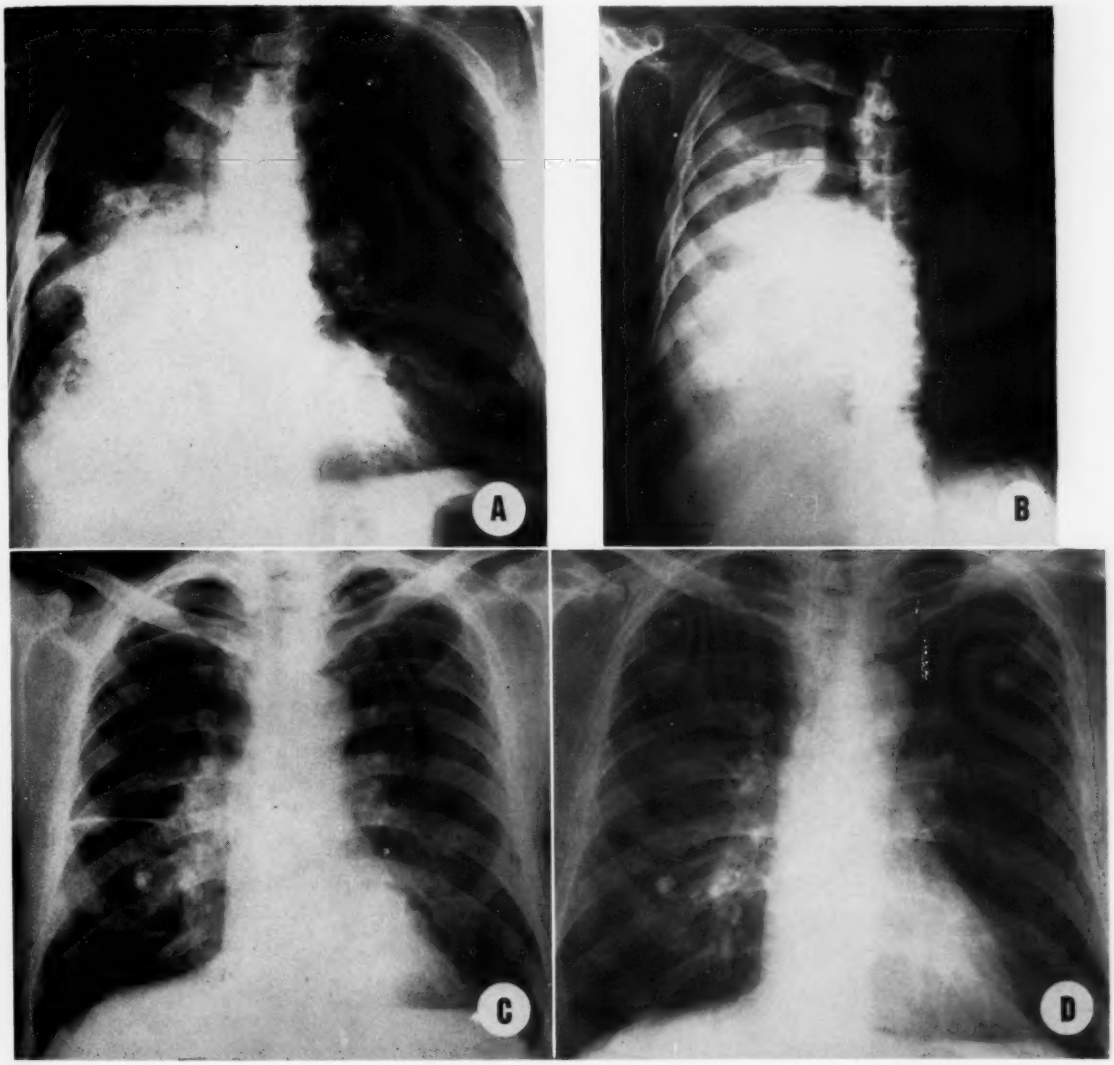

Fig. 2. Sixty-seven year old white male. Heavy smoker. Chest pains, slight hemoptysis, weight loss of 15 pounds in the last month. Weak, confined to wheel chair. (*A*) October 6, 1954. Irregular massive shadow in the right middle and lower lobes. Right main bronchus plugged by tumor mass (poorly differentiated carcinoma). (*B*) October 27, 1954. Advanced massive atelectasis. Complete obstruction of right main bronchus. (*C*) December 2, 1954. Near completion of Betatron therapy: bronchial lumen freed, atelectasis, retractions disappeared. Residual tumor masses in the right hilar and carinal area. Thickened upper interlobar fissure. (*D*) December 28, 1954. Four weeks after completion of Betatron therapy: no gross evidence of residual tumor. Also regression of clinical symptoms. Started to work. (Died nine months after treatment of widespread metastases, including bilateral pulmonary dissemination.)

which had been temporarily "protecting" the eroded vessels. Only 1 patient is living, apparently free from disease for over two years (Fig. 3); another for six months; and others are living but in an indefinite status as to residual or recurrent tumor. Irradiation is worth while in spite of these dismal figures for two reasons. The first is that the treatment frequently modifies the course of the disease, the lumen often becomes patent and larger, and the patient gains strength for variable intervals. The second reason is that surgery cannot offer better results. Four cases have been studied in considerable detail at autopsy; 2 showed no residual tumor, 1 showed metastases

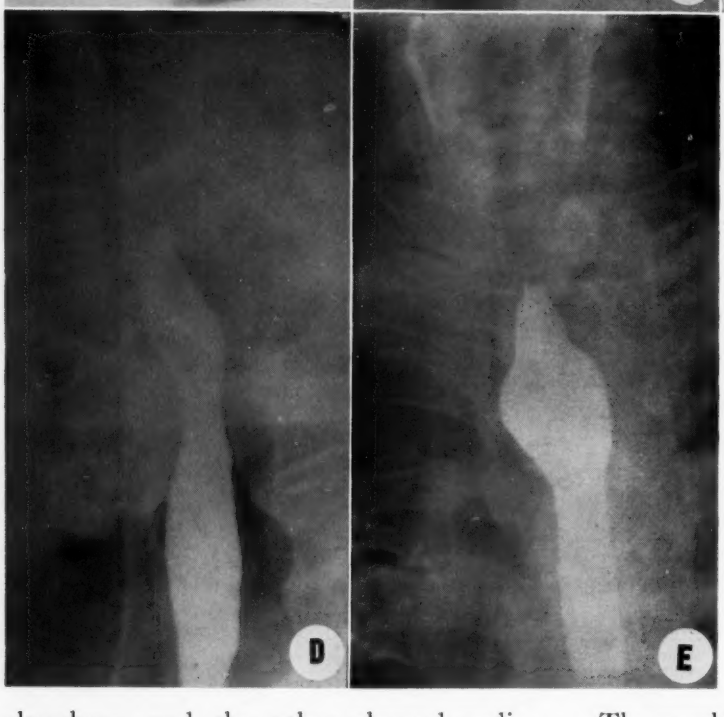

FIG. 3. Seventy-eight year old white male. Diabetes, cerebral arteriosclerosis, dysphagia for two months. (*A*) Lateral neck film: widened prevertebral soft tissue shadow bulging slightly into the tracheal shadow. (*B*) Barium filling: irregular tumor mass in the posterior wall of the cervical esophagus pushing the anterior wall into the trachea, as in *A*. (*C*) Eighteen months after Betatron therapy: the prevertebral shadow regressed to normal width. Normal air bubble in esophagus. (*D* and *E*) Barium filling at the same time: smooth, normal esophageal outlines, with slight narrowing at site of the original lesion. Apparently healed. No clinical findings or symptoms thus far, twenty-eight months after treatment.

elsewhere, and the other showed radiation pneumonitis. Surgical exploration of another patient disclosed the treated area to be entirely healed but an active lesion was found below the zone of treatment. He died of postoperative pneumonia before we could treat this lower segment.

The esophageal group could benefit most from further improvement of the technique since it is in this group that we have seen the most serious radiation damage in neighboring normal tissues.

The next group comprises the *less deeply situated B group lesions* such as in head and

neck areas. The 29 brain tumors were quite diversified as to location and histologic type. The curative results in these cases were not basically different from those observed in cases treated by lower voltage roentgen-ray beams. Excluding intrasellar lesions, only 1 patient has survived more than four years without apparent tumor. The other patients died within two years, either from recurrence or radiation damage. However, the palliative effect was more impressive, the immediate side effects were much less, and there is preliminary evidence that certain types had longer and more useful survival than one would expect with conventional roentgen therapy. Several of the patients who succumbed one to one and one-half years after treatment showed radiation damage and not residual tumor as cause of death. For this reason we rarely give second courses of treatment to brain tumor patients if the residual tumor is not proved histologically.

The 24 other head and neck cancer cases yielded final results quite similar to those obtained with lower voltage roentgen therapy. The advantages of the very high energy treatment seem to be less discomfort for the patient, less risk of cartilage or bone damage, and fewer late damages in the superficial tissues. Of the 8 larynx cases, 4 are living without evidence of disease, 1 for more than five years.

The group of abdominal cases is small partly because of the limited amount of material referred to us, partly because many of the cancers in this area are relatively radioresistant, and finally because of the anticipated difficulty of delivering an adequate and uniform tumor dose without causing considerable upset to the patient and serious late intestinal changes. We have seen some good palliative effects and some possible cures, but thus far are not as much encouraged about megavoltage therapy use here as elsewhere in the body.

The third possible indication for highly penetrating radiation is represented by our *C group of patients with evidence of widespread or generalized cancer.*

At times we saw patients with such widespread cancer or other generalized diseases that we tried spray irradiation of large portions of the body with palliative intent. We aimed at slowing down the progress of disease, prolonging life, and possibly shortening the most distressing part of the terminal stage. In many cases these trials were unsuccessful, but we did see a few examples of excellent palliation (Fig. 4), some patients having regained a temporary useful life for several months. In many cases life did not seem to be prolonged but suffering became less severe and the terminal episode was shortened.

Thirty-eight patients have been exposed to spray irradiation techniques. Five had very extensive lesions involving a large body segment, 20 had widely disseminated metastases, and 13 had multicentric systemic disease. The dosage is obviously the greatest problem in this technique, and we give as much as the patient can tolerate. Of course, the more uniform distribution of the very high energy radiation in the body not only destroys more cancer uniformly in more areas, but it also subjects normal radiosensitive tissue to more damage since depth location does not afford much protection.

The Betatron also yields an *electron beam* which we have described in earlier papers.[1,3] Only 33 patients have been treated with this beam and since it is not as penetrating as the roentgen-ray beam at the same energy level, it was used in more superficial lesions. The main advantage of the electron beam seems to be a more precise dose distribution to a desired area, at the same time sparing adjacent and underlying normal tissues from unnecessary exposure (Fig. 5).

Several times in this discussion we have alluded to late manifestations of damage to normal tissues unavoidably irradiated either because they were so close to the tumor that they had to be included in the maximum tumor dose area, or were coincidentally in the path of the beam. These damages can be briefly listed as follows:

In treating apical lung tumors one may

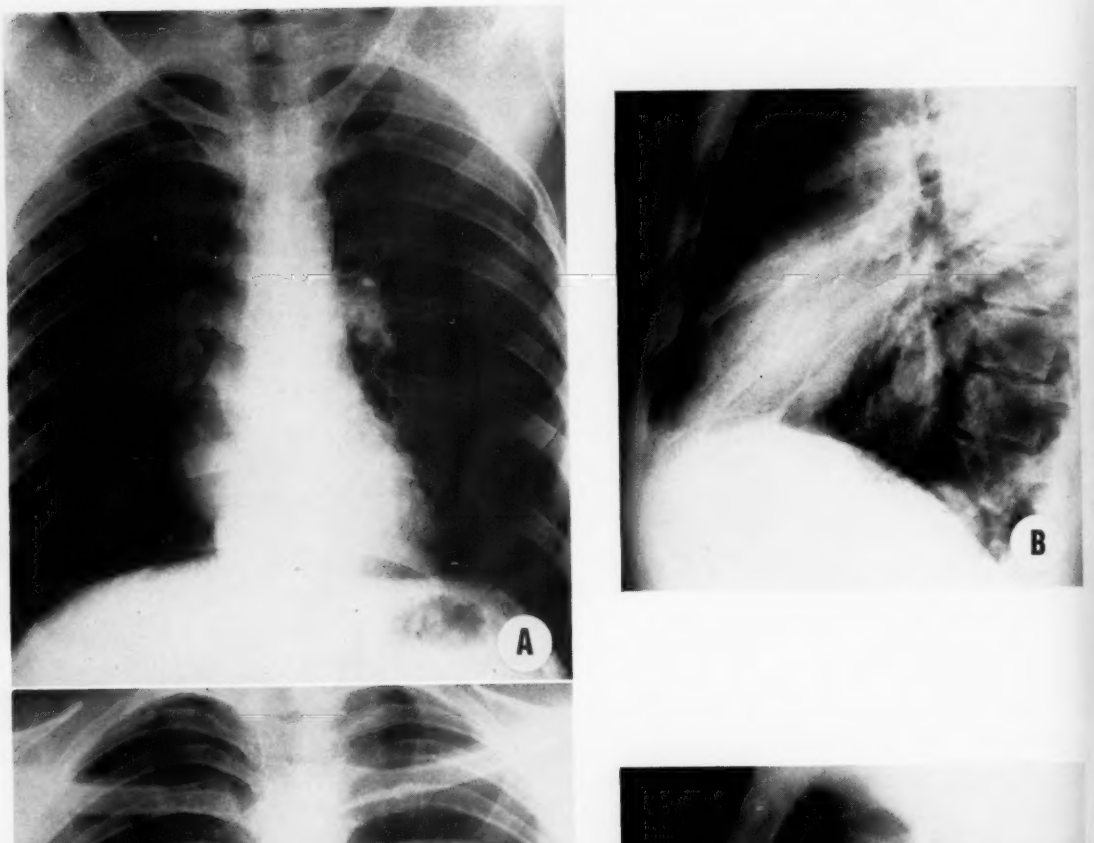

FIG. 4. Twenty-three year old white male. November, 1948, Ewing's sarcoma of right femur; regression after roentgen therapy. May, 1952, recurrence, disarticulation of right hip. (*A*) May 12, 1952. Postero-anterior chest roentgenogram. A few large metastatic nodes superimposed on the heart shadow. Several small nodes in the left lung field (the print does not show all the faint opacities). (*B*) Lateral view at the same time. Shows the large nodes in the inferior mediastinum and in the posterior medial lung segments. (*C* and *D*) August 27, 1952. After Betatron spray therapy. All the nodes disappeared roentgenologically. (Recurrent lung nodes after one year. After further intermittent irradiations, the patient expired of generalized metastases on April 18, 1955, disabled only in the last month of life.)

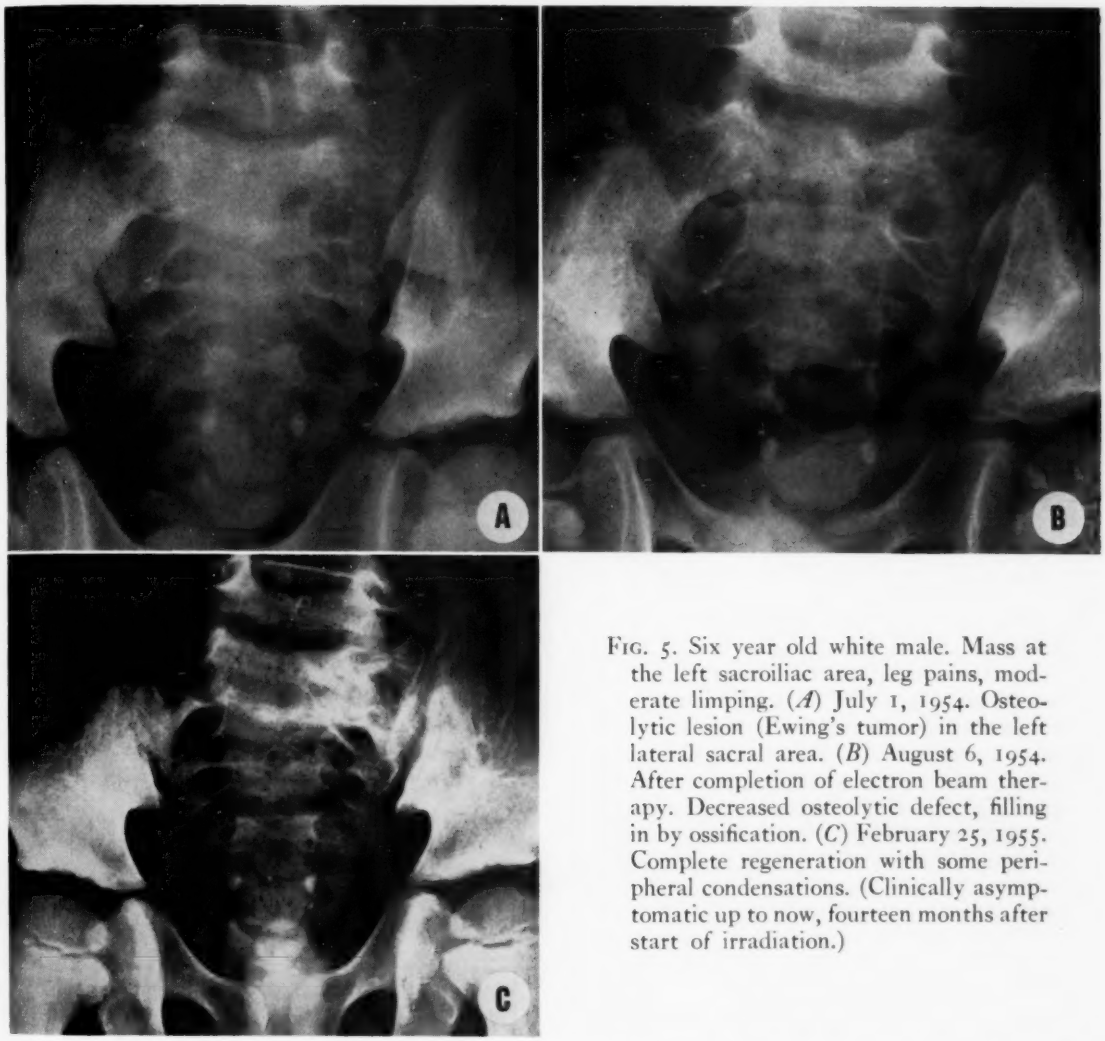

Fig. 5. Six year old white male. Mass at the left sacroiliac area, leg pains, moderate limping. (*A*) July 1, 1954. Osteolytic lesion (Ewing's tumor) in the left lateral sacral area. (*B*) August 6, 1954. After completion of electron beam therapy. Decreased osteolytic defect, filling in by ossification. (*C*) February 25, 1955. Complete regeneration with some peripheral condensations. (Clinically asymptomatic up to now, fourteen months after start of irradiation.)

eventually encounter fibrous induration of the lower neck tissues, including the brachial plexus; radiation myelitis of the spinal cord; and various degrees of atrophy. Treatment of bronchogenic carcinoma may lead to atrophy and thinning of the esophagus with perforation, especially if its wall was involved by the tumor originally, and to mild or moderate radiation pneumonitis. The treatment of esophageal carcinoma most commonly produces moderate to severe radiation pneumonitis; perforation of the esophagus is most often related to original weakening of the normal structures by the tumor. Treatment of brain and spinal cord tumors can result in degeneration and necrosis of nerve tissue. Pelvic irradiation has led to variable degrees of chronic colitis, and narrowing of the sigmoid colon and rectum. In no patient have we seen undesirable late complications in skin and bone.

We should stress that we see identical damages following conventional radiation therapy and that these are not strictly the sequelae of megavoltage therapy. There are several reasons why these damages are more frequently associated, falsely, with new types of radiation:

1. There is more interest in these patients and they are followed more closely by the person who treated them.

2. More of these patients live long enough to develop complications.

3. Administration of an adequate higher tissue dose occurs in a relatively greater number of patients under megavoltage regimen than with conventional methods.

4. Radiation complications arising from our routine therapeutic procedures are often falsely classed clinically as tumor recurrence by those who are not aware of the similarity of symptoms from radiation damage. Observations on material from the megavoltage range are helping to improve the accuracy of differential diagnosis between tumor recurrence and radiation damage.

In summary, there is a very definite place for Betatron therapy in clinical cancer management. Its advantages are largely related to spatial distribution of dose. The increased benefits and longer survival certain patients obtain should not be marred by risk of chance of late radiation damage. These risks are not out of proportion to those encountered in adequate therapy with conventional roentgen rays, and can be reduced by indicated work yet to be done in the area of optimal time-dose relationship.

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University of Illinois Hospital
Chicago, Illinois

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DISCUSSION OF PAPERS BY DR. FLETCHER, DRS. BURKELL AND WATSON, AND DRS. HAAS AND HARVEY

Dr. Franz Buschke, Seattle, Washington. I had the privilege to study at leisure the manuscripts of the papers just presented. Each one contains many more observations and stimulating suggestions for further thought and investigation than could be included or absorbed in the condensed versions read this morning. I cannot, of course, discuss the many details which would deserve further analysis, and shall limit myself, therefore, to a somewhat aphoristic presentation of a few thoughts which the synoptic meditation—if I may say so—about the trends expressed in these papers has stimulated.

I would like to recall that to the best of my knowledge the only bona fide bronchogenic carcinomas controlled by radiation therapy for more than five years are 6 patients of Smithers treated with 400 kv. rotation, and 1 person of my personal knowledge, reported by Scharer, treated in Zürich in 1941 with 180 kv., through 4 fields, who is still well.

Similar situations in regard to the treatment of other neoplastic conditions could easily be cited. They are, of course, not meant to suggest that these conditions should now be preferably treated with 180 kv. They illustrate, however, two important points which I again would like to emphasize (1) that the biologic character of the disease determines the therapeutic result to a greater degree than the particular voltage used, and (2) that with proper adjustment of the radiotherapeutic technique to fully utilize the advantages and minimize the disadvantages of a particular quality of rays, different voltage ranges are interchangeable for most clinical situations. Dr. Fletcher has most appropriately emphasized that technical procedures which have proved useful in one level cannot be transferred into another. The number of instances in which, in the hands of equally competent therapists, the use of a specific voltage range is crucial is too small to expect statistically significant differences of curability.

Another point of importance which I would like to emphasize is in relation to the better tissue tolerance of radiation of shorter wave lengths. While the better protection of normal tissue—either because of a more favorable distribution of the radiation through the body or because of a truly better tolerance of certain tissues for comparable doses—is admittedly one of the most important advantages of the higher voltages, this difference should not be overrated. The tolerance levels that have been recognized by previous experiences with medium voltage therapy in general must still be respected. The observations of the Saskatoon group with regard to the tolerance of the

laryngeal cartilage for supervoltage radiation has reconfirmed the experience that the introduction of appreciably higher doses than those found tolerable in the medium voltage range for particular tissues is not tolerated and leads to a point of diminishing return. The need for physically accurate determination of dose distribution prior to treatment has become more urgent with increasing voltages because the clinical guides useful in medium voltage therapy, namely, the observation of mucosal and skin reactions, are less reliable in these voltage ranges. This has occasionally led to an overemphasis on physical calculations to the neglect of a sufficient appreciation of individual variations of tolerance. A physically correct preconceived plan, important and valuable as it is, should be considered only as a general guide subject to change during the course of therapy, depending on the careful observation of the individual response in regard to tumor regression, tissue reaction, and general tolerance.

These remarks are not intended to minimize the importance of supervoltage and megavoltage therapy; but an attempt to demonstrate statistically a superiority of certain voltages for the treatment of certain neoplastic situations with the aim to arrive at rigid indications for the use of certain qualities of rays will rather becloud the true progress which the individually well-adjusted use of the higher voltages has made possible. It is even less realistic to attempt the demonstration of a general superiority of one particular machine compared to another. It is more important that each therapist familiarize himself thoroughly with the physical characteristics and the biologic effects of the radiation at his disposal and with the relative advantages and disadvantages of the particular machinery in order to allow for them when planning treatment. If it is at times possible to conduct treatment in a somewhat more elegant fashion by using one type of machine rather than another, we would consider such finesses as tid-bits for the radiologic gourmet of remote practical significance. If the patient were permitted to choose, the points to consider from the aspect of curability of his disease would be in decreasing order of importance, the type of disease, the radiotherapist, and last and least, the type of machine.

DR. WILLIAM E. COSTOLOW, Los Angeles, California. I shall confine my remarks to the consideration of Cobalt-60 teletherapy and two million volt roentgen therapy. In our institute we have used Cobalt-60 teletherapy for three years and two million volt roentgen therapy for two years. I should like first to discuss the presentation of Drs. Burkell and Watson. Our observations have been so similar to those of these authors that much I could say would be repetition. We are using a similar amount of Cobalt and an uncomplicated type of apparatus. We too have found the apparatus simple in use in obtaining higher tumor dosage. Also, we are attempting the radical treatment of certain tumors, which previously would have been treated only palliatively. When giving tumor dosages of from 6,000 to 8,000 r, we have been using a fractionation over a period of from six to seven weeks or more. To give these large dosages in from three to four weeks only leads to troublesome radiation complications.

Time does not permit discussion of the various types of lesions treated by Cobalt-60 teletherapy, but I would like to briefly mention one type which was not mentioned by Drs. Burkell and Watson. This is intraoral cancer. We have treated some 40 cases of intraoral carcinoma with Cobalt-60 and have been impressed by the primary results obtained. Fourteen cancers of the floor of the mouth have been interesting. During the past thirty years we have used glass, platinum, and gold radon seeds, low intensity platinum needles, and intraoral roentgen therapy combined with conventional external high voltage roentgen therapy. We have seen arrests in cases treated by all these methods, but with the Cobalt-60 teletherapy the consistency and regularity of disappearance of the primary lesions in the floor of the mouth, including those of 5 cm. in diameter or more, have been very significant. It is possible to treat these patients through 10 by 10 cm. or 10 by 15 cm. opposing fields, securing a tumor dose of from 6,000 to 8,000 r. A daily tumor dose of from 170 to 240 r is given five days a week. Patients with bone infiltration and necrosis have shown poor response to treatment, and practically all of these cases have been failures. Our present routine is to advise the radical or "commando" type of operation for such cases. However, our experience with Cobalt-60 teletherapy leads us to believe that all patients having intraoral cancer bone involvement or necrosis should be offered radiation therapy before radical surgery is proposed.

In our present treatment of lung cancer we are using two million volt roentgen therapy in most cases in order to utilize larger fields. Portals should be employed which include the primary tumor and mediastinal lymph nodes. This is, of course, an important principle in the treatment of any tumor—the lymph nodes and lymphatic drainage should be treated. We make portal films in all cases and believe this is an important point in technique. The entire involved lung from the level of the diaphragm to the cervical region, the mediastinum, and both supraclavicular areas are treated. The uninvolved lung and larynx are blocked out. The daily tumor dose averages 170 r and the treatment is carried to a tumor dose of from 6,000 to 7,000 r in from forty to forty-five days. We do not believe lung fibrosis is a consideration. Most of the lung cases we see are advanced. Palliation with freedom of pulmonary involvement and symptoms is the goal. The majority of these patients succumb from brain or liver metastases. Marked palliation was obtained in many cases of lung cancer, with some apparent arrests in the past two to three years.

Our present technique in carcinoma of the cervix is to use Cobalt-60 therapy (70 cm. distance—four 10 by 15 cm. fields over the pelvis) giving 2,000 r tumor dose at Point B in twenty-five days. This is followed by radium application, intra-uterine and in the vaginal vault, using the James F. Nolan modification of the Manchester type of applicator. The treatment is given in two seances two weeks apart. The total tumor dose at Point A is approximately 6,500 r, and at Point B 3,500 r. The total treatment time is from forty-five to fifty days. We realize that with Cobalt-60 a larger dose could be given at Point B, but we are still using the dosage mentioned above.

Both Cobalt-60 teletherapy and two million volt roentgen therapy through large fields or rotation are used in the treatment of advanced cases of bladder carcinoma. We believe that large fields, often a 10 by 14 cm. circular field to include lymphatics and extensions, are indicated here. Tumor doses of from 6,000 to 8,000 r in from six to eight weeks have been used. Complete regressions have occurred in some cases. Practically all have shown some palliation if complete treatment has been given. We are using cytologic studies from the urine as developed by Ruth Graham to follow the progress of patients under treatment. In one case the urine did not become negative for cancer cells until a bladder tumor dosage of 8,956 r had been given over a period of eight weeks.

As pointed out by Drs. Haas and Harvey, the optimal dosage and time relationship in megavoltage therapy have not been too definitely determined. Additional study will be needed; however, these papers show that good progress is being made.

DR. IVAN H. SMITH, London, Ontario, Canada. Drs. Haas and Harvey have been most modest and yet their pioneer studies in the clinical use of the Betatron are familiar to all.

It is with Cobalt-60 therapy that the London, Ontario Clinic is particularly familiar and a comparison of our observations with those of the Saskatoon Group may be of value at this time. Drs. Burkell and Watson are keen observers. Their appraisal of results is in no way tinted by uncontrolled enthusiasm, and their Canadian colleagues in the East are fully aware of their determined wish to contribute exact information in the newer radiotherapeutic fields.

Their statement pertaining to the use of the plaster jacket with intervening wax bolus as annulling the skin sparing effects of Cobalt-60 therapy deserves a comment. Theoretically, this is true but in practice it is seldom a problem. Our plaster of paris jacket beam directed thorax cases seldom experience more than a faint erythema; nor do the skin reactions in the oral or laryngeal cases create any concern. A little juggling with the number and direction of portals amply enables the operator to take full advantage of the skin sparing effects and with added wax and plaster enables one to straighten out isodose curves and fix the beam precisely.

Drs. Burkell and Watson stated that, as a rule, it has been possible to deliver with Cobalt-60 therapy a tumor dose 10 per cent higher than with conventional roentgen therapy. By this I understand that the local tissues will tolerate the 10 per cent increase with no increase in the severity of reaction. I am convinced it is even much greater than this in specific sites, with larger fields, and in certain patients, but I wonder if the doctor has experienced the sensation or intuition that perhaps the dosage *has* to be increased by 10 per cent to achieve the same lethal tumor effect.

I am most impressed with the simplicity of technique, patient comfort, and dosage advantage at Point B, by using Cobalt-60 therapy

routinely as is done in Saskatoon, in carcinoma of the cervix. This is a nice clinical object lesson, a preferred plan of attack and surely will pay increased five year dividends.

Drs. Burkell and Watson have a unique breast cancer group for follow-up study. Might I ask, why do they think by lowering the central tumor axillary dose from 4,400 r to 4,200 r and the parasternal dose from 4,950 r to 4,200 r, that the incidence of pulmonary reactions will be appreciably altered? I am disturbed, yes, harassed, by the incapacitation occasionally produced by pulmonary fibrosis.

Intrinsic carcinoma of the larynx, thus far, is our most impressive curable group. I wonder if the term "cartilage necrosis" hasn't served its period of usefulness in teaching everyone to strive for homogeneity of dosage. True, it must be more common in high spot overdosage but it can also occur with low dosage. What I really feel we are dealing with is laryngeal suppuration, a complication dependent mainly upon tumor invasion with concomitant infection; indeed, irradiation coincidentally can play its part but not until the stage is set. The word necrosis, particularly if whispered by a radiologist, implies to our colleagues irreparable radiation damage. In passing might I suggest, for better professional relations, that we use the less incriminating term "laryngeal suppuration."

During 1952 and 1953 we treated radically 12 persons with intrinsic carcinoma of the larynx. Two of these developed laryngeal suppuration. The stage was set for one, I believe, in that he had been treated years before by roentgen therapy for laryngeal papillomata. Shortly following treatment a biopsy was made through the skin in an effort to determine whether the extralaryngeal induration was malignant, and immediately following this a fistula developed and cartilage sloughed away. The patient, however, is quite well two years following therapy. Our second case of suppuration received 5,000 r in four weeks and ten months subsequently developed edema, required tracheotomy and died at two and one-half years with recurrent cancer in the larynx. I would suspect that at the ten month period there might well have been residual burrowing cancer responsible for his so-called cartilage necrosis.

Our basic laryngeal technique was a plaster of paris collar with built up wax portals using three fields, one anterior and two posterolateral. The spinal cord dosage has been of no concern being in the range of 3,000 r. Each field, naturally, was localized roentgenographically. The field sizes varied from 5 by 5 cm. to 6 by 8 cm. and occasionally larger. One case was treated by a single field and I do believe this simple technique will play an important role if the time comes when we are granted the privilege of irradiating the Stage 1 cancer confined to the vocal cord. One case initially had a metastatic lymph node in the neck; all others, however, had intrinsic lesions which extended beyond solitary cord involvement and were staged as II; hence, laryngofissure could not have been utilized in this group and laryngectomy was the only alternative to irradiation.

Ten cases of the 12 are free of disease from one year ten months to three years four months following treatment. The single field case received a tumor dose of 7,000 r in four and one-half weeks. The largest dosage was 7,000 r in an over-all period of thirty days, 6,800 r in thirty-one days, 6,000 r in four weeks, 5,500 r in three and one-half weeks. There was slight dysphagia and I think, to say the least, sore throat was an annoying nuisance. Tracheotomy for reaction was not required in any instance. The Saskatoon results are certainly excellent. I think it is interesting that we, too, have switched from the three to four week technique in favor of a dose quite similar to that of Saskatoon, 6,000 r to 6,500 r in five to six weeks. The two-field technique with the wedge filter is a very sound and commendable development but I would predict that neither this nor any other technique will completely eliminate laryngeal suppuration. Actually, there is little need to quibble about small variations in techniques which deliver reasonable homogeneity of dosage. All must agree that despite physical perfections certain cancers are just downright "ornery."

Drs. Burkell and Watson stated, in their section on cancer of the lung, "we look upon this treatment as palliative and think it is well worthwhile"; whereas, Drs. Haas and Harvey took the attitude that "as the result of these experiences there are relatively few patients we approach with palliative intention." In general, we would certainly agree with Drs. Haas and Harvey. Our greatest problem in designing therapy for the bronchogenic carcinoma is the biologic question of "how extensive is the disease." What size of area do we treat? Do we use through and through fields

and stop at a moderate dosage? Do we include the entire hemithorax where the dosage must of necessity be a little less, or in some cases do we elect to beam directly or rotate taking in a volume smaller in extent but to a much higher dosage. Each year will gather important information for us on this very subject. At the present time if we can conceive of a tumor within an 8 cm. volume, we accept for a curative dose and aim for 5,000 r to 6,500 r in five to six weeks. Since commencing our Cobalt work, October 27, 1951, we have treated 33 such patients radically; 4 of these are alive eighteen to thirty-eight months later. During this same period we had 96 very advanced cases which we treated palliatively, ofttimes including one entire lung field. Strangely enough, of this group, which received in the neighborhood of 3,000 r to 4,000 r in three to four weeks, 4 are alive fourteen to twenty-seven months later.

Another group of tumors which has been touched on today by various authors is carcinoma of the esophagus. Here, again, we have some "ornery" varieties. This is a challenging group, a disheartening group, but we must keep our heads up, working diligently until that day when something comes along to supersede either radiation therapy or esophagectomy. In contrast to our own experience with conventional roentgen therapy we are willing to state that Cobalt-60 beam therapy is a distinct improvement in the treatment of this lesion. In 1952 and 1953, 14 cases were teated by radical dosage averaging 5,000 r in three weeks to 6,500 r in six weeks. Four of these cases are alive without evidence of disease, and for the most part without any symptoms, sixteen to twenty-eight months later.

In closing, I believe we all sense that the optimal wave length band in clinical supervoltage and megavoltage application is a broad one, and that friendly competition among those trying different spectra should work to the betterment of the patient.

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THE PRIMARY TREATMENT OF ADENOCARCINOMA OF THE RECTUM BY HIGH VOLTAGE ROENTGEN RAYS (1,000 KV.)*

By I. G. WILLIAMS, M.B., F.R.C.S., F.F.R., *and* H. HORWITZ, M.B., B.S.
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DURING the last ten years very little has been published in the European or American literature on the treatment of adenocarcinoma of the rectum by roentgen rays. The following paper sets out to report results of 189 cases so treated at St. Bartholomew's Hospital, London, between the years 1937–1954, and based on this experience, to define the position of high voltage roentgen therapy as a primary method of treatment.

Surgery remains the treatment of choice and undoubtedly offers the patient his best chance of cure in this otherwise mortal disease, and it is not our contention that roentgen therapy is an alternative to surgery in the treatment of the "early" case. The abdominoperineal resection of Miles, nowadays usually a synchronous combined procedure, remains the most successful of all methods of operative treatment, and is the most generally practiced form of therapy throughout the world. However, a large number of more or less formidable operations, including some which conserve the sphincter mechanism in suitable growths, have their various indications and are practiced by many surgeons.

Other nonsurgical approaches to the problem include:

1. Diathermy fulguration (Kergin[6] 1953, Strauss and others[11] 1935, Thorlakson and Hay[12] 1938).
2. Contact roentgen therapy, practiced fairly extensively by continental workers (Chaoul[3] 1944, Albot, Parturier-Albot[1] 1951, Parturier-Albot and Tsilliras 1951,[10] and others).
3. Surface and interstitial radium application.
4. Conventional deep roentgen therapy (now almost totally abandoned in Great Britain).
5. Rotational therapy (Vogel[13] 1952).
6. High voltage roentgen therapy and telecurie therapy.

The first three methods are theorectically unsound for any but superficial or early lesions, *i.e.*, those best treated by radical operation. Of the other methods, we believe that after surgery high voltage roentgen therapy is the best method of treatment and offers the patient an excellent chance of alleviation of symptoms and some chance of cure.

COLOSTOMY

In the management of inoperable adenocarcinoma of the rectum, colostomy is only indicated when intestinal obstruction occurs or is imminent. In other circumstances colostomy does not prolong life (Wyard[14] 1925). Its palliative effects are limited, and in many cases it may add a further burden to the already unhappy lot of the patient with severe and distressing symptoms due to a large rectal neoplasm. Only insofar as it reduces secondary infection does it relieve symptoms; pain from pressure, tenesmus from tumor mass, and mucous discharge and bleeding from the growth often continue almost unchanged in severity after colostomy. In such cases palliative excision of the rectum may be justified to relieve symptoms even in the presence of distant metastases. This type of palliation may help a patient spend his last few months in a comparative degree of comfort.

When colostomy is performed in a case to be treated by roentgen therapy, it is

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advisable to make the usual left "inguinal" colostomy a little higher on the anterior abdominal wall than is customary, since with the technique to be described, a treatment field is often brought in at the left inguinal region, and a "high" colostomy does not handicap planning.

SELECTION OF CASES

Surgery being accepted as the treatment of choice where the attempt is to cure the patient, the "selection" of cases for roentgen therapy largely resolves itself into an acceptance of all surgical "rejects." These, however, do not represent a large proportion of the cases seen by the surgeon. At St. Mark's Hospital for Diseases of the Rectum, the resectability rate for all cases has been over 90 per cent in the last few years. However, basing figures on the 1949 British Empire Cancer Campaign analysis, one of us (Williams[15] 1949) estimated that 70 per cent of cases are incurable by surgery when first diagnosed, and will, therefore, require treatment in addition to surgery or primary treatment other than surgery. Of the cases referred to our clinic, it was found possible to give treatment to all but a very small number, mainly terminal cases with very widespread disease, or those with severe secondary infection.

The patients treated fall into three main groups: (1) Operable cases, which by reason of age and/or infirmity are judged unfit to withstand a major surgical procedure. (Thus for reasons other than the disease under consideration, the expectation of life in this group is limited.) (2) Patients judged inoperable clinically or found inoperable at laparotomy. (Over 80 per cent of cases treated fall into this group.) (3) Patients who refuse operation. (This is a very small group.) Radical roentgen therapy is not without its discomforts and disadvantages, and a variable local reaction with a mild or moderately severe general reaction is to be expected in all cases during treatment. It is not an easy alternative to surgery as far as the patient is concerned, and some fortitude may be called for during the latter half of treatment.

MATERIAL

Patients were in the main referred by the Surgical Staffs of St. Bartholomew's Hospital, and St. Mark's Hospital for Diseases of the Rectum, to whom we are indebted for allowing us to study these cases. An attempt was made to classify them into four groups according to the extent of the disease. The classification was made either on clinical grounds or on laparotomy findings. Pathologic classification into grade of malignancy was not attempted. Although clinical assessment has its limitations, it is believed that the accompanying table (Table 1) represents a fair analysis of the extent of the disease in the material studied, at the time of treatment. Thus it will be seen that some 82 per cent of cases were in an advanced stage of the disease. All these patients suffered from adenocarcinoma of the rectum and were treated primarily by high voltage roentgen therapy.

TABLE I

TOTAL NUMBER OF CASES—189

		Cases	Per Cent
Stage I	Lesion confined to rectal mucosa but not penetrating rectal wall	8	4
Stage II	Lesion involving whole thickness of rectal wall but not extending beyond these limits	26	14
Stage III	Lesion spread beyond rectum to neighboring structures and/or involving regional lymph nodes in the pelvis	128	68
Stage IV	Carcinoma of the rectum with distant metastases	27	14

TABLE II

AGE AT COMMENCEMENT OF TREATMENT IN 189 CASES

Years	Cases	Per Cent
20–29	5	3
30–39	10	5
40–49	26	14
50–59	46	24
60–69	57	30
70–79	37	20
80–89	8	4
Average age 60 years		
Female	56	30
Male	133	70

Cases treated for disease recurrent after operation, and for squamous cell growths of the anal canal are not included in this study.

AIMS OF TREATMENT

Many of the advanced cases included in this series might have been considered suitable for symptomatic treatment only; however, radical treatment was almost always given and a dose of 6,000 r to the whole of the tumor-bearing volume in six to eight weeks was aimed at, although not always achieved. Treatment short of this dose was extended to the limits of tolerance as judged by skin and mucosal reaction in each individual case. By aiming at "cure" even in advanced cases, excellent palliation was very often obtained, and the patient's life was prolonged and made more comfortable. The incidence of early or late radiation ill effects was reduced to a minimum by careful and judicious assessment of each individual case during treatment. Factors necessitating curtailment or interruption of treatment included cystitis, colitis and enteritis, since the viscera concerned lay partly in the paths of the beams. In women a vaginitis with discharge usually occurred during treatment. Skin reactions arose towards the end of the course and were especially severe in the regions of the vulva, perineum and anus because of the greater sensitivity of the skin of these areas, but with high voltage therapy were seldom severe enough to warrant curtailment of treatment. General reactions were usually mild.

METHOD

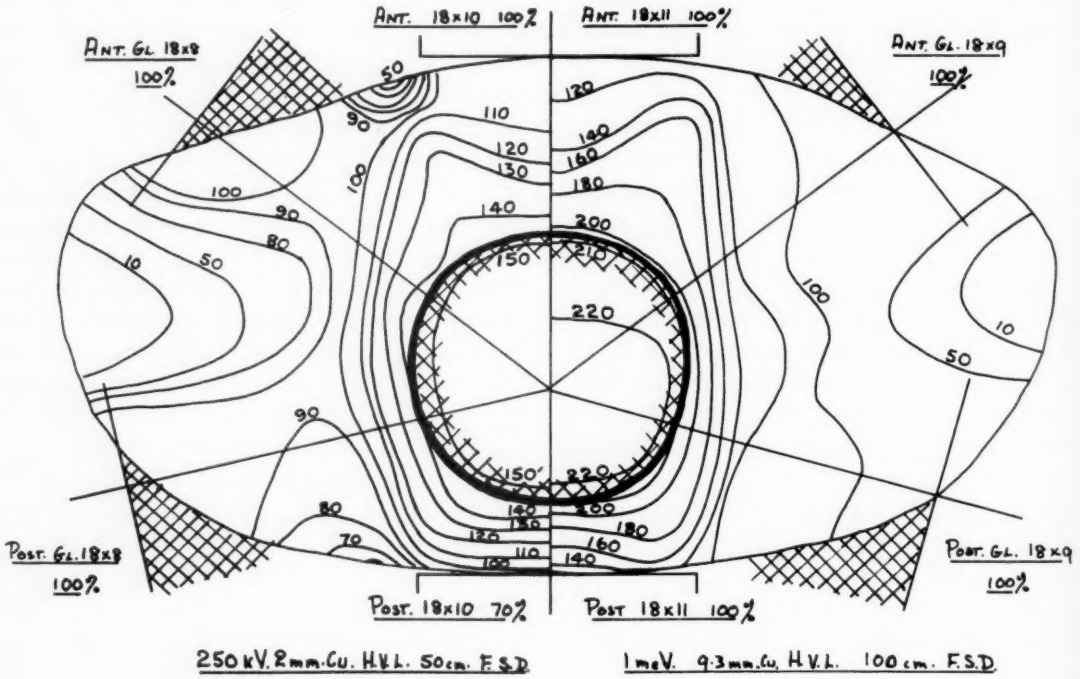
All cases were treated with roentgen rays generated at 1,000 kilovolts (half value layer 9.3 mm. copper). The gain in depth dose with high voltage over the conventional 200–250 kv. roentgen rays is considerable, and with a five or six field crossfire technique using an anterior and posterior port with corresponding anterolateral and posterolateral ports each of the order of 16 by 10 cm., it is possible to deliver a depth dose to the whole of the true pelvis of the order of 120–140 per cent of the skin field dose. High voltage has further advantages to offer in the pelvis, since roentgen rays generated in the 1,000 kv. range show no marked differential absorption in bone, and thus the presence of the pelvic girdle introduces no gross errors into depth dose calculations and can be neglected in the drawing-up of isodose charts. A homogeneous heavy irradiation of all the pelvic tissues is thus achieved. Although with this technique the region of the femoral neck is not included in any direct beam, the danger of radiation effect in this area is very slight with high voltage roentgen rays. Avascular necrosis of the femoral neck was not observed in any of the patients in this series.

The tumor cells are scarcely more radiosensitive than normal mucosa; however, an impression was obtained that the papillary type of adenocarcinoma showed a better response to irradiation than other types. Dosage is therefore critical and for this reason, treatment in each case has to be carefully planned and executed. Cases must be considered individually and the possibilities of late radiation ill effects must be weighed carefully against the advisability of treating to the limits of tolerance.

The position and size of the lesion are determined accurately by clinical and roentgenographic means and the block of tissue to be irradiated is defined. Individual isodose charts are drawn up for all patients. A tumor dose of 6,000 r in six weeks is prescribed, treatment being carried out five days per week. Patients are seen daily throughout their treatment by a medical officer and a watch is kept for severe local or general reactions. Blood cell counts are performed regularly although in practice it is found that leukopenia and anemia are never severe enough to occasion interruption of treatment. General measures are of course important and skilled nursing care is essential. The patients are encouraged to take an adequate diet which is supplemented by vitamins. Anemia if present is combated by the usual remedies, including blood transfusion if necessary.

RESULTS

It is difficult to interpret the results in a series such as this since most cases were in an advanced stage of their disease and in poor general condition. Some were in poor health by reason of disease other than carcinoma of the rectum, and thus the expectation of life in this group was limited by two or more diseases. It is of course impossible to convey in cold mathematics what the relief of distressing symptoms has meant to many of these patients. An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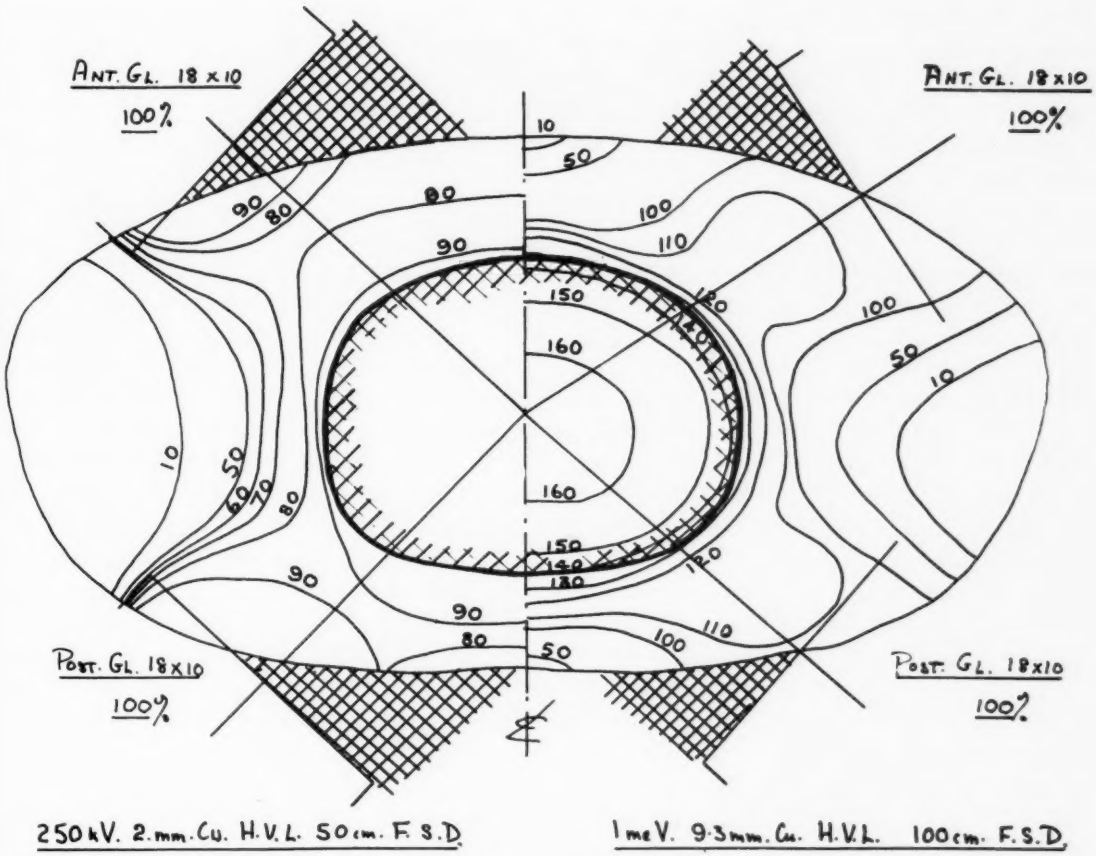
POST. 18x10 70%
POST 18x11 100%
250 kV. 2mm. Cu. H.V.L. 50cm. F.S.D.
1 meV. 9.3mm. Cu. H.V.L. 100 cm. F.S.D.

ISODOSE CHART 1. This chart contrasts the dose distributions for the two qualities of roentgen rays specified. The section is taken through the pelvis in a case of carcinoma of the rectum, and the central area bounded by the thick line represents the tumor-bearing area to be treated.

	250 kv.	1 mev.
Skin dose per field per 1,000 r tumor dose	720 r	475 r
Maximum skin dose per 1,000 r tumor dose	775 r	665 r
Integral dose per 1,000 r tumor dose	9.0 megagram roentgens	7.1 megagram roentgens

The 1 mev. portion of the chart represents approximately the true dose distribution. The 250 kv. chart takes no account of differential absorption in bone, fat, etc.



ISODOSE CHART 2. This chart illustrates the contrast in dose distribution of the roentgen rays of the two qualities specified when the whole of the true pelvis is treated in a case of advanced carcinoma of the rectum.

	250 kv.	1 mev.
Skin dose per field per 1,000 r to true pelvis	1,090 r	740 r
Maximum skin dose per 1,000 r to true pelvis	1,090 r	800 r
Integral dose per 1,000 r to true pelvis	8.8 megagram roentgens	4.8 megagram roentgens

As in Isodose Chart 1, the 250 kv. plan is probably inaccurate since differential absorption in bone, fat, etc., has not been allowed for.

attempt is therefore made to assess results on the following points: (1) Relief of symptoms due to the primary growth; (2) avoidance of colostomy; (3) avoidance of severe early or late radiation ill effects; (4) clinical cure and survival figures.

Relief of Symptoms Due to the Primary Growth. In this study, symptoms have been considered individually, as the symptom-complex in each patient was different and expressed differently according to the patient's mental attitude. The four main symptoms were pain, tenesmus, mucous discharge and bleeding; other symptoms, such as diarrhea, constipation, incontinence, etc., were variable and moreover were modified sometimes by colostomy and often by treatment. No attempt has been made to assess on the response of the patient as a whole to the treatment, but it was found in general that when the cardinal symptom was relieved other symptoms diminished coincidentally, and the patient's general well-being improved pro-

portionately. This was not entirely true when bleeding was the main symptom. The effect of irradiation on a bleeding tumor is well brought out in the table. In some cases although bleeding was stopped, other symptoms were not relieved or only partially relieved. The incidence of symptoms and their response to treatment is summed up in Table III. In assessing subjective phenomena, such as pain and tenesmus, caution is necessary, since the psychologic component, different for each patient is always present. This applies to a lesser extent in considering mucous discharge and bleeding, which, however, are more objective in their manifestation. Therefore, only three simple assessments have been adopted: Complete relief, partial relief, and no relief. The greatest measure of success was achieved when bleeding was the presenting symptom, and in some 90 per cent of cases bleeding was either completely arrested or relieved. In contrast to this, when mucous discharge was predominant, 67 per cent of patients obtained some measure of relief. For pain and tenesmus the percentages in whom relief was obtained lay between these two figures. As might be expected, it was found that relief of symptoms paralleled clinical regression of the tumor mass. In cases where objective regression was marked the measure of relief from symptoms obtained was proportionately good and in cases showing little regression of the tumor the degree of relief was poor.

TABLE III

	Present	Completely Relieved	Partially Relieved	Not Relieved
Pain	102 cases	49 (48%)	29 (29%)	24 (23%)
Tenesmus	66 cases	36 (55%)	12 (18%)	18 (27%)
Mucous discharge	116 cases	47 (41%)	30 (26%)	39 (33%)
Bleeding	135 cases	103 (76%)	18 (14%)	14 (10%)

Avoidance of Colostomy. As previously stated, in all cases colostomy was avoided for as long as possible and in many cases when shrinkage of the tumor occurred as a result of therapy, obstructive symptoms disappeared and colostomy no longer needed to be considered. In a few cases it was found possible to close a colostomy after treatment had been completed, as the primary growth had disappeared leaving a clinically normal rectum. These were cases with a localized proliferative primary lesion with some super-added infection and inflammation, and they tended to do well.

The number of cases on whom colostomy was performed was 112 (59 per cent). The number of cases not requiring colostomy was 77 (41 per cent). In cases in whom colostomy was not performed the sole method of treatment was roentgen therapy. In the remaining 112 cases (59 per cent) colostomy was performed (a) either before or after treatment to relieve obstruction; (b) when the rectum was removed for residual or recurrent disease after a full course of roentgen therapy (9 cases); and (c) for post-radiation fibrosis induced in the intestinal wall.

Avoidance of Early or Late Radiation Ill Effects. In some 50 per cent of the patients, treatment was not straight-forward and had to be interrupted and modified because of radiation reaction, *i.e.*, in these cases it was found impossible to deliver the full planned treatment in the prescribed time. The reactions mostly comprised bladder and bowel irritations, and to a lesser degree general malaise, nausea and vomiting, etc. Leukopenia was rarely of sufficient severity to stop therapy. These setbacks were generally simple to deal with and in no case did they represent, in themselves, a serious hazard to the patient. As far as bladder and bowel reactions were concerned the critical dose was in the region of 2,000 r, *i.e.*, at the end of the second week of treatment.

FIG. 1. Rectum removed from a male aged forty-seven. Symptoms had been present for ten months before the diagnosis was made. Biopsy showed a well differentiated adenocarcinoma, and the lesion was considered inoperable at that time. A total of 4,625 r to whole of tumor bearing area was given in five weeks. Abdominoperineal excision was performed six weeks later for obstructive symptoms. The specimen shows a thickening, mainly in the mucosa, 15 cm. from the anal margin (A), which had caused considerable narrowing of the lumen. The histologic features are shown in Figure 2.

The late complications, however, were more serious. Fistulae, mainly rectovaginal developed in 12 patients (6 per cent) and chronic radiation necrosis occurred in 9 cases (5 per cent). In these conditions it was difficult to be certain whether uncontrolled malignant disease was not at least partially responsible, or that destruction of neoplasm had not left a gap which adjacent tissues, devitalized by heavy irradiation, were unable to close.

Fibrosis occurred in 32 cases (17 per cent) and produced a stenosis of the rectum. Many of these patients already had a

FIG. 2. This section was taken at the region of the stricture (A in Fig. 1). Much fibrosis is seen in the rectal wall, and there is a breach in the main muscle coat. The mucous membrane shows a small ulcerated area, the base of which is infiltrated with well differentiated adenocarcinoma. This infiltration extends into the submucous layer. Deeper in the wall, and on the peritoneal aspect, no trace of neoplasm can be found. Sections of 10 lymph nodes removed with this specimen showed some to have undergone fibrosis. In none was there evidence of secondary neoplasm.

This patient is alive and free from this disease two and one half years after the original diagnosis was made.

colostomy because of obstruction due to neoplasm, but of the others, the development of fibrosis, because it interfered with the structure and function of the rectum, made colostomy necessary. Following treatment, fibrosis takes place in the whole intestinal wall and this is further increased by the late vascular changes. A dense narrow rigid tube replaces the rectum and the organ cannot function properly. Stricture formation, *i.e.*, localized fibrosis occurs most commonly at the site of the neoplasm, but it may occur in the irradiated normal anal canal below a carcinoma of the rectum.

Clinical Cure and Survival Figures. This should be considered in conjunction with the age of the patients, and the presence or absence of other diseases. In the following tables (Table IV and V) no corrections have been made for these factors. One hundred and sixty-five cases were treated in the years 1937–1949. Of these 33 per cent survived two years, 14 per cent for three years, and 5 per cent for five years. Ten per cent of the 156 deaths within the first five years were due to intercurrent disease.

Of the 9 patients who were alive at the end of the five year follow-up, 6 died at varying periods from five to ten years (including 4 of intercurrent disease) and 3

TABLE IV

	Total	2 Year Survivals	3 Year Survivals	5 Year Survivals
Stage I	5	2 (40%)	—	—
Stage II	21	10 (48%)	4 (19%)	2 (10%)
Stage III	115	40 (35%)	17 (15%)	7 (6%)
Stage IV	24	3 (12%)	2 (8%)	—
Total	165	55 (33%)	23 (14%)	9 (5%)

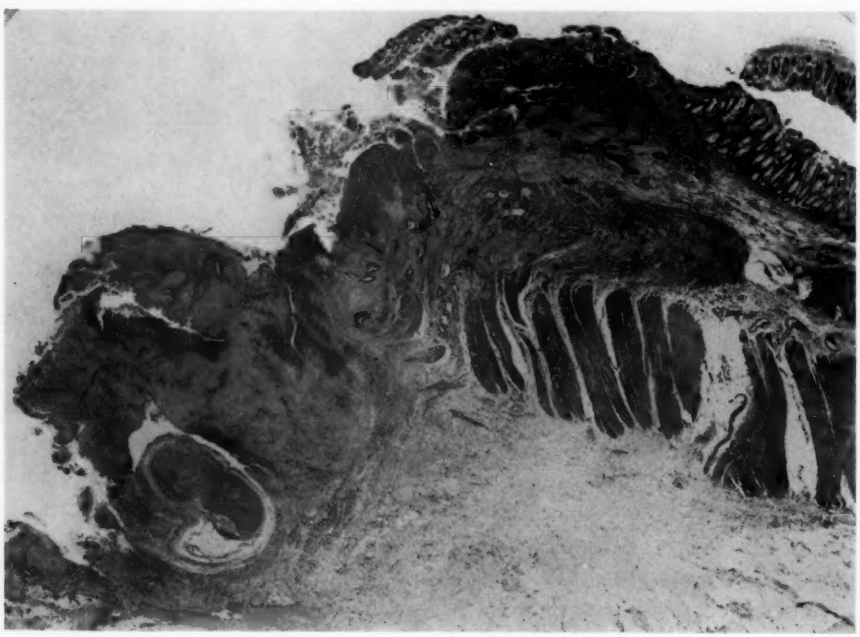


FIG. 3. Section of rectum removed six weeks after a full course of high voltage roentgen therapy for clinically residual disease. A process of diffuse fibrosis is seen, which extends through the rectal wall into the surrounding tissues. At the ulcer edge are a few small scattered areas of apparently viable and moderately well differentiated adenocarcinoma. Sections of 14 lymph nodes removed with this specimen showed none to be involved by secondary growth.

Table V

	Stage I	Stage II	Stage III	Stage IV	Total
Total	7	25	123	28	183
2 Year Survival	3 (43%)	13 (52%)	41 (33%)	3 (11%)	60 (33%)

were alive at the end of 1954 having survived for eleven, twelve and sixteen years, respectively. All these were Stage III cases. Of the 15 cases which died of intercurrent disease within the first five years, some were clinically free from carcinoma of the rectum at the time of death. The two year survival figures for 183 cases treated in the years 1937–1952 are given in Table V.

Of 123 deaths recorded in the first two years 8 per cent were due to intercurrent disease. These figures do not differ appreciably from other published data and thus it appears that roentgen therapy does not increase the average expectation of life in advanced carcinoma of the rectum, except perhaps in those fortunate cases in which distant metastases have not yet occurred, and full control of the local disease has been achieved by irradiation. Thus a small number of complete cures are possible and have, in fact, been obtained.

Daland, Welch and Nathanson[4] (1936) give the average survival with colostomy alone as 16.9 months from the onset of symptoms, while Cade[2] (1950) gives the average survival as 12–18 months from the establishment of the diagnosis. Many other writers give similar figures. The absolute figure for five years surgical cure is only in the region of 12–15 per cent.

Removal of the Rectum after Full Roentgen Therapy

In 9 cases operations were carried out for removal of the rectum after a full course of roentgen therapy for residual disease (Fig. 3), or for disease recurrent after an interval of time. Surgery in these cases was made technically possible by the regression of the growth produced by irradiation. Pathologic reports and histologic sections are available in these cases and some postmortem material is also available and these together will form the subject of a further communication.

In one patient operated upon fourteen months after treatment, for ulceration and recurrent bleeding, no trace of cancer could be found in the intestinal wall, the lesion being a small area of radionecrosis. This patient died in the postoperative period from peritonitis. In a second case a dense fibrous scar formed at the site of the neoplasm with a few viable-looking islands of carcinoma at the periphery (Fig. 1 and 2).

Summary and Conclusions

One hundred and eighty-nine cases of adenocarcinoma of the rectum are reported and their treatment by high voltage roentgen rays is outlined. One hundred and fifty-five (82 per cent) of these cases were advanced and inoperable, while in the remaining 34 (18 per cent) operative treatment was contraindicated for one reason or another. We believe that this method offers such patients real benefit, which in a few cases may be long lasting.

The following results may reasonably be expected from the treatment:

1. Complete or partial relief from symptoms due to the primary growth.
2. A good chance of avoiding a colostomy.
3. A small but definite chance of "cure."

The incidence of early and late radiation ill effects is described. The possibility of development of serious radiation effects cannot be forecast for any individual case, but in a series such as this, it is almost inevitable in a small number of cases if treatment is carried out energetically and determinedly. This possibility has to be faced, if worthwhile results are to be obtained in a large proportion of patients treated. The critical factor appears to be the tolerance of the normal healthy tissues. It is considered that the better therapeutic

effect in this disease of the shorter wavelength roentgen rays compared with roentgen rays generated in the conventional medium voltage range is not due to any difference in biologic effect, but due to the increase in depth dose obtained and a greater facility with this technique for homogeneous irradiation of the pelvis. The results should therefore be equalled or bettered by the larger supervoltage units now in use and by large telecurie units.

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VOL. 76, NO. 5

NOTES ON THE ISODOSE CURVES FROM A 2 MEV. VAN DE GRAAFF MACHINE*

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THE commercial 2 mev. Van de Graaff machine† as delivered to this institution was fitted with a set of adjustable collimators mounted directly below the lead "pot" surrounding the target of the roentgen ray tube. The maximum distance between the anode and the distal edge of the collimators was 40 cm. Investigation of the unit revealed an output of 76 r/min. at 100 cm.; 12.5 mm. Cu half value layer; central axis depth dose data similar to those already reported in the literature, and summarized by Wheatley;[6] and a focal spot size of 9 mm. The therapy at this institution is carried out chiefly with conventional stationary fields with the machine in an approximately vertical position and the patient prone. Ability to have variable field sizes within the maximum field size limit is regarded as a desirable feature. Collimation therefore should be done by adjustable collimators fitted to the machine and not by an additional collimating system supported on extension rods screwed into the forward face of the unit as appears customary where rotation therapy is the prevailing mode of treatment. Therapy is conducted at 100 cm. target skin distance.

It was assumed that at this energy quality changes in roentgen ray flux take place with varying depths, but that they are small, perpendicular to the axis of the beam. Isodose curves were plotted by a combination of ionization chamber and film techniques. The central axis depth dose data were obtained by ionization chamber methods and the off center dose rate by means of the film technique. Type M film was used enclosed in a masonite cassette with film wrapping paper between the cassette and the film. This was found to be necessary to avoid fine mottling of the film. The cassette was then mounted in a masonite phantom so as to be in the plane of the principal axis of the roentgen beam. Exposures were chosen so that the resulting densities were within the linear range of the film (less than 2). The film densities were measured with a Weston Model 877 Type 5 densitometer with a sensitive spot of 1.5 mm. diameter. Off axis densities were expressed as a fraction of the central axis density at the same depth in the phantom; this in turn was known to correspond to a certain percentage depth dose from the ionization chamber measurements. Check runs with an ionization chamber for 5×5 cm. and 10×10 cm. fields gave equivalent results within experimental error (±2 per cent) up to depths of 20 cm. Accordingly, the method was adopted as being within clinically desirable accuracy with the advantage of consuming minimum machine time.

Ionization chamber measurements were made with a chamber of 3 mm. internal diameter and 8 mm. long, connected to a negative feed back amplifier described by Fedoruk, Johns and Watson.[1] The chamber was tracked in a water phantom 30 cm.[3] with the long axis parallel to a field edge by a servo mechanism operated from outside the room. A second chamber connected to a similar amplifier was used to monitor the output. Both chambers were connected to similar amplifiers and recording millivoltmeters and their output recorded. The unit was returned to zero output between movements of the chamber, thus keeping a check on any movements in the zeroing of the amplifier and ancillary systems and forming a convenient method of marking off the different readings. The chambers were constructed of bakelite, carbon, polystyrene and alumi-

* From the Tumor Institute of the Swedish Hospital.
† Van de Graaff unit provided by research grant of the National Cancer Institute, U.S.P.H.; support for physics research received from Damon Runyon Cancer Research Fund.

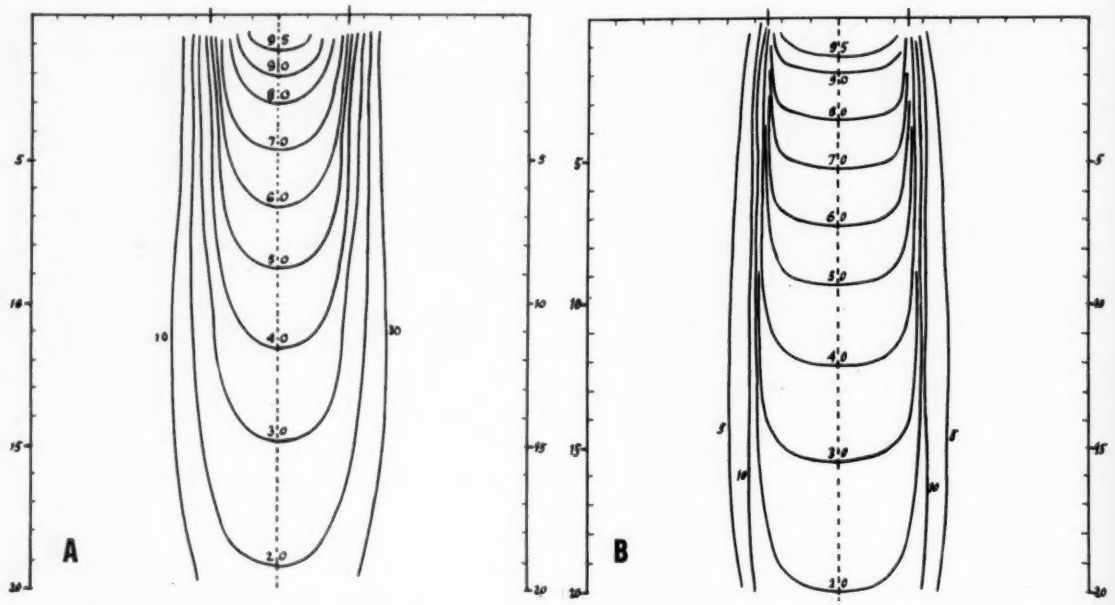

FIG. 1.(*A*) Isodose curves for field 5×5 cm., 100 cm. target skin distance, 60 cm. collimator skin distance. (*B*) Isodose curves for field 5×5 cm., 100 cm. target skin distance, 25 cm. collimator skin distance.

num, and were found to be wave length independent from 12.5 mm. Cu to 2 mm. Cu half-value layer when compared to a Victoreen chamber of known characteristics.

The isodose curves obtained were similar to those reported in the earlier literature[3,4,9] and were judged disappointing when compared with those obtained on the 800 kv. machine (Fig. 1*A* and 2*A*). Examination of the geometry of the collimator, etc. revealed that such disappointing curves are to be expected with the collimator-

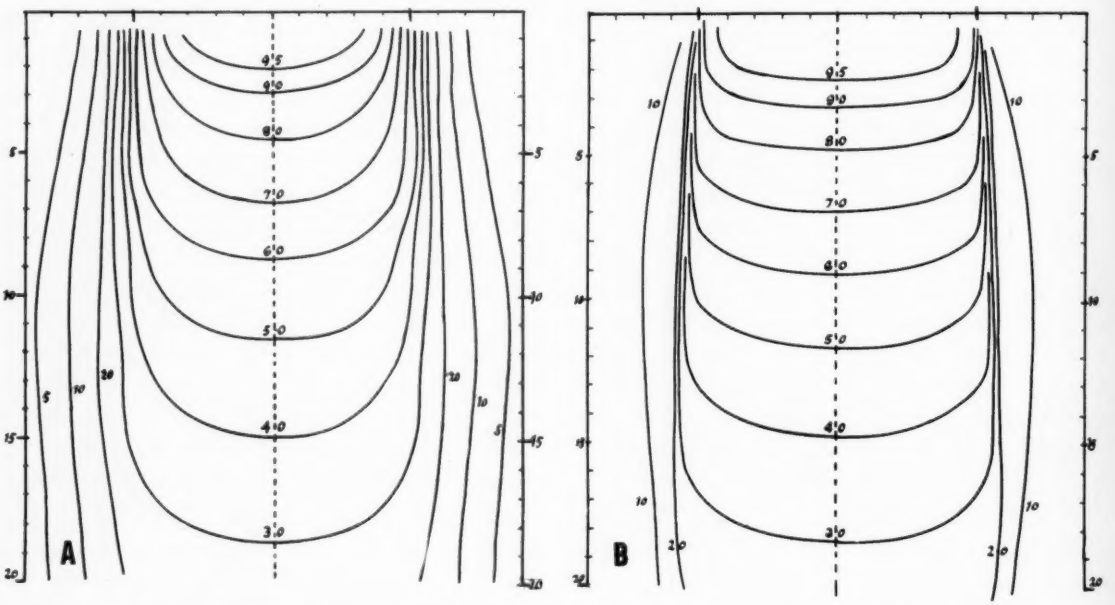

FIG. 2. (*A*) Isodose curves for field 10×10 cm., 100 cm. target skin distance, 60 cm. collimator skin distance. (*B*) Isodose curves for field 10×10 cm., 100 cm. target skin distance, 25 cm. collimator skin distance.

focus and collimator-skin distance at such a disadvantageous ratio.

Two approaches were possible: (1) to reduce the target skin distance to a minimum, and (2) to maintain the target skin distance at approximately 100 cm. and move the collimator closer to the skin. The second approach appeared more advantageous since, owing to the thickness of the collimator (3 inches of lead), arrangement 1 would improve the isodose curves in one axis, but improvement in the axis at right angles to this would not be marked. Two sets of isodose curves would then be necessary and care would need to be exercised in positioning the pairs of collimators relative to the clinical field so that the "best" curves were aligned in the most critical direction. Approach 1 was adopted as an interim measure while arrangements were made for the mechanical fulfillment of approach 2.

The skin sparing effect of the 2 mev. radiation, due to the maximum ionization being attained at a depth of 3–4 mm.[5] was judged to be an important attribute of this type of equipment. It was also known that this effect can be reduced by contamination of the roentgen ray beam with secondary electrons from the collimating system.[2] It was desirable, therefore, to determine the minimum collimator skin distance which retained the desirable features of electron build up.

No suitable ionization chamber being available, the problem was investigated by means of films and a step wedge of mix. D. wax, details of which will be reported elsewhere.

The results obtained were in good agreement with those reported by Miller,[3] Howarth and co-workers,[2] Wilson and Perry,[7] and Trump,[5] using ionization chambers under similar circumstances (Fig. 3). From these data 25 cm. was chosen as the distance providing acceptable build up conditions and sufficient clearance to the field on the patient. Therefore as an interim measure a target skin distance of 65 cm. was employed. An extension piece was

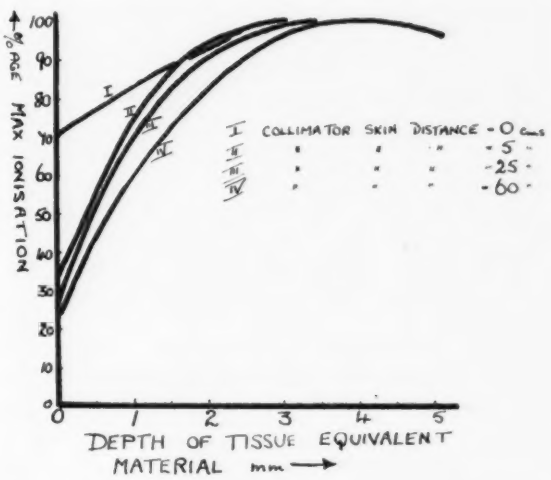

FIG. 3. Curves showing the variations of ionization build up with different collimator skin distances, but a fixed field size of 15×3 cm. and a fixed target skin distance of 100 cm.

designed and constructed to insert between the "pot" surrounding the anode and the adjustable collimator (Fig. 4, 5 and 6). This unit consisted of two steel plates of 2 inch stock, machined to reproduce (1) the bottom of the pot when the rotating bearing carrying the collimator assembly was removed, and (2) the top surface of the rotating bearing and collimator unit both having $6\frac{1}{2}$ inch circular central apertures. These two plates were welded coaxially to an 11 inch long and $\frac{1}{2}$ inch thick standard steel tube of 10 inch external diameter which was lined with 1 inch lead. This heavy gauge material was employed to ensure mechanical rigidity and to guard against an increase in leakage radiation from the head. The extension piece was then bolted to the main pot with the bolts which had retained the rotating bearing. The bearing itself carrying the collimator assembly was bolted to the lower plate. This permitted easy adjustment of field size and enabled rotation of the field at will. The maximum field size obtainable at 100 cm. target skin distance was 15.5 cm. × 16 cm. This was judged clinically satisfactory. When larger fields are required, the target skin distance can be increased to 120 cm. In general, very sharply defined

Fig. 4. Machine before insertion of extension piece.

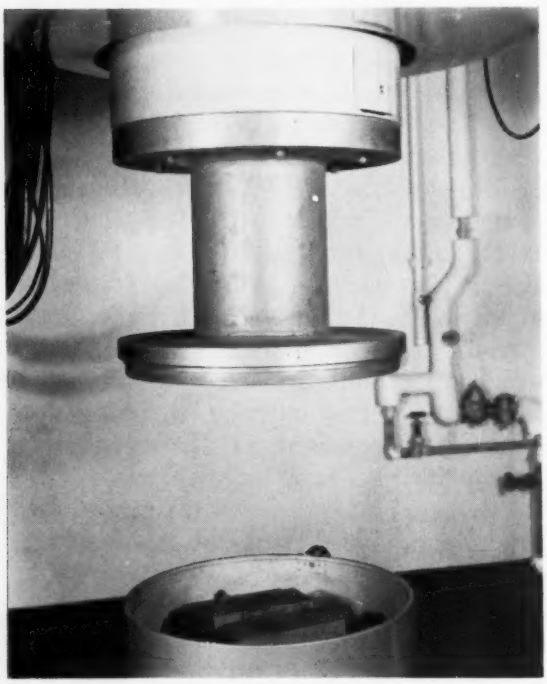

Fig. 5. Extension piece.

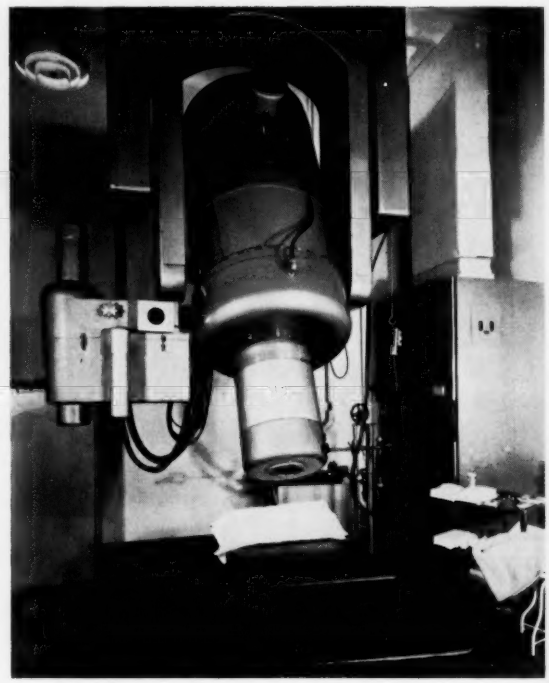

Fig. 6. Machine after insertion of extension piece.

beams with this size of field are not so essential and this arrangement was considered acceptable. This extension piece increased the focus-collimator distance to 75 cm. and the treating distance was returned to 100 cm. target skin distance. Isodose curves were plotted by methods outlined before. Curves for fields of 5×5 cm. and 10×10 cm. are shown in Figures 1*B* and 2*B*. They can be seen to constitute a notable improvement over those in Figures 1*A* and 2*A*.

It would appear that the shape of the isodose curves to be expected from a supervoltage machine is dependent not only upon the voltage, filtration, target skin distance, and focal spot size, but also on the target collimator, and the collimator skin distance ratio, and that isodose curves obtained with all other factors being equal are not applicable unless the necessary adjustment is made.

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Our thanks are due to Mr Dale Trout for machining the step wedge. The extension piece

was manufactured to our design by Pacific Steel Products of Seattle.

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FIELD LOCALIZATION FOR BETATRON THERAPY*

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FOR treatment by external irradiation, accurate localization can be obtained by the use of a light localizer or treatment cone to delineate the entrance beam and by exposing roentgen ray film to check the exit beam. A light localizer is particularly useful when corners or edges of the roentgen-ray beam must be blocked by means of external diaphragms located between the unit and the skin. The Allis-Chalmers 24 RCM Betatron in use at this hospital was supplied with plastic treatment cones designed to show the field size at the appropriate target skin distance. In general, these treatment cones have been found satisfactory. In a few instances, however, either the anatomy of the treatment area or the need for external diaphragms has prevented their use. To meet these treatment conditions, an externally mounted light localizer was designed.

As a final check on the accuracy of localization it is often the practice to expose roentgen films in the exit beam. In this institution, these roentgenograms are obtained with the patient in treatment position, using the therapy unit as the source of roentgen rays. When a Betatron is operated at 22 mev., there is very little difference between the absorption of the beam in bone and tissue. Consequently, if routine roentgenographic techniques are followed, the resulting contrast is too low to be seen. We have found that by the proper choice of technique, roentgenograms can be obtained with sufficient contrast for localization purposes.

EXTERNAL LIGHT LOCALIZER

Because of space limitations within the Betatron collimating system, it was thought to be impractical to attempt mounting a light localizer within the unit. With the exception of one mirror, the light localizer now in use (Fig. 1) is attachable to the outside of the unit by means of two mounting studs and thumb nuts in the same manner as the treatment cones. The alignment of the light beam was found to be reproducible using this method of attachment.

The geometric arrangement (Fig. 2) consists of the light source, S, and two first surface mirrors, M_1 and M_2. Light from the source is reflected from M_1 which is mounted at an angle of 45° to the direction of the light beam. The reflected light passes into the collimator and is, in turn, reflected from a second mirror, M_2, which is attached to the unit beyond the end of the interchangeable collimator. The image of S in M_2 will lie at the focal spot of the Betatron, F, if the distance $SM_1+M_1M_2$ is equal to the distance M_2F. If the size of S is comparable to that of the focal spot, its image will approximate the focal spot in both size and position.

Although the square shadow produced by mirror M_1 in the center of the light pattern was found useful in that it marked the center of the field, its size should be kept to a minimum to prevent restricting the use of small fields. The minimum size of mirror M_1 is determined by the distance SM_1 and the size of the largest roentgen-ray field. The projected area of M_1 on a plane perpendicular to the axis of the collimator and through the center of the mirror should not be less than the cross sectional area of the largest roentgen-ray beam at a distance SM_1 from the focal spot. Otherwise M_1, acting as a diaphragm, will restrict the

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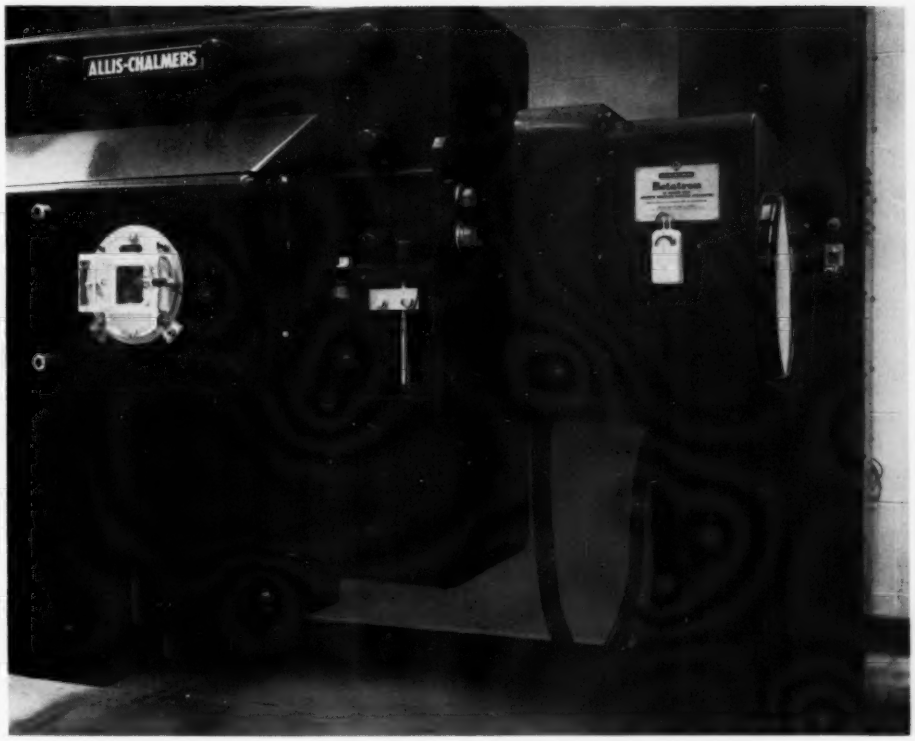

Fig. 1. Photograph of Betatron with light localizer attached.

light beam to areas smaller than the maximum desired. The area of M_2, of course, must be of sufficient size to cover the smaller opening of the largest collimator. When the above conditions are fulfilled, the light beam from any size collimator will accurately represent the roentgen-ray beam from the collimator.

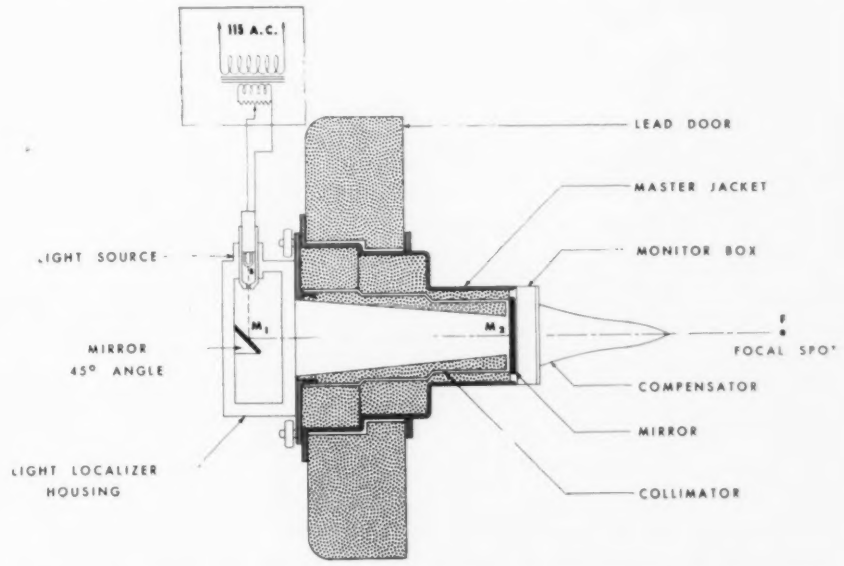

Fig. 2. Schematic diagram of Betatron collimating system, showing geometric arrangement of light localizer.

DETAILS OF LIGHT LOCALIZER

The focal spot of the Betatron is about 0.1 mm. by 0.3 mm. in area. As a compromise between the intensity of the light beam and the size of the geometric penumbra, a larger light source was used. It was found that the best compromise was a No. 222 miniature flashlight lamp with a lens end bulb, selected for proper filament-lens alignment. For the bulb now in use, the source of light, which is the image of the filament formed by the lens, measures 2 mm. by 0.7 mm. At 120 cm. target skin distance the geometric penumbra of the light beam along an axis of the field is equal to the dimension of the light source along that axis. In order to keep extraneous light from reaching the treatment area, the bulb is enclosed in a cylindrical collimator which restricts its light to a cone of sufficient size to cover the front mirror. Voltage is applied to the filament through a National Electric current controller. The life of the bulb is extended by always increasing the voltage from zero up to the rated value.

A first surface mirror was chosen as the front reflector in order to avoid unnecessary errors due to refraction and as the back reflector in order to avoid the effects of radiation on glass. The glass of the latter mirror, being in the roentgen-ray beam at all times, is soon darkened by radiation. When using a first surface mirror, this darkening will not affect the light intensity. The efficiency of the mirror has not been noticeably affected by radiation after a dose of 2,000,000 r to the mirror.

FILM LOCALIZATION

Early attempts at this hospital to use film localization with the Betatron followed standard diagnostic techniques. The roentgenograms obtained by these methods were found to be of insufficient contrast. In order to obtain the contrast necessary for localization roentgenograms, it became apparent that films having high contrast characteristics would be needed. Because of their fine grain and high contrast characteristics, Eastman type M and Ansco type B films were found to be the most suitable. Using this type of film in a cardboard cassette and with the Betatron operated at 22 mev., an investigation was made to determine the optimum loading, exposure, and processing conditions. The experimentation with film technique was carried out with a human pelvis and rubber balloon, representing a bladder, suspended in a one-cubic foot water phantom to simulate the pelvic region. The balloon was filled with different contrast media including barium and air.

Although roentgenograms could be obtained using this technique, the exposure times were long (about one minute). Through the use of commercially available lead intensifying screens in a rigid cassette, the exposure time was reduced by a factor of 3. These screens have the added advantage of increasing the quality of the roentgenograms while decreasing the exposure time. Optimum results were obtained by using a 0.050 inch lead sheet in intimate

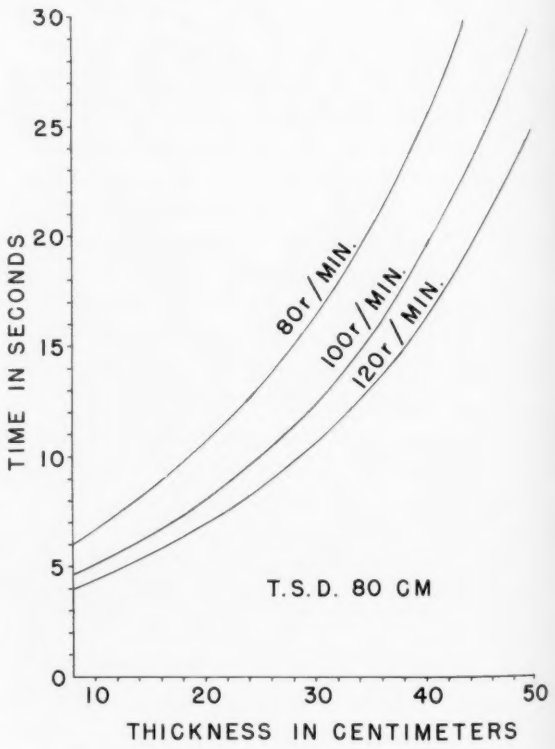

FIG. 3. Exposure chart for 80 cm. target skin distance.

contact with the film as a front screen and a 0.010 inch lead sheet as a back screen. The best roentgenograms of the "bladder" were obtained when the balloon was filled with air. For full development and maximum contrast, a development time of eight to twelve minutes is recommended. However, in order to process the films by the routine procedures of the diagnostic department, a shorter development time is used. This shorter time, five minutes, does not seriously impair the quality of the roentgenograms.

For the convenience of the operator, exposure charts have been made (Fig. 3). The exposure time is determined by the Betatron dose rate, the target skin distance, and the percentage transmission through the patient. When using a five minute development, it is desired that the exposure time be such as to deliver about 5 r to the front face of the film cassette. This will give a film density of approximately 2.0. The dose delivered to the patient is considered as part of the treatment dose which follows after the exposure has been made. The roentgenogram shown in Figure 4 is typical of those now being obtained routinely under treatment conditions.

DISCUSSION

An externally mounted light localizer has a disadvantage with respect to one mounted within the unit in that it must be removed

Fig. 4. Anteroposterior roentgenogram of pelvis, showing 50 cc. of air in the bladder and catheter.

before treatment begins. Its use, however, is not restricted to a particular unit, as long as geometric requirements are met, and it has been found of advantage for treatment conditions in which treatment cones could not be used. When used alternately with treatment cones, its method of attachment and its accuracy can be made the same as that of the cones. A permanently attached light localizer is now under construction in which the light source and front mirror are moved into position, as a unit, by a sliding motion.

The extremely small focal spot (0.3 mm.) of the Betatron lends itself readily to sharp, highly definitive roentgenography. The quality of the roentgenograms obtained when using the technique outlined above will depend upon the care used in handling and processing. At 22 mev. the detrimental effects of pressure marks or weak chemicals will be much greater than those occurring at lower energies. For film localization purposes, it is not necessary to obtain a roentgenogram of diagnostic quality. The quality of the roentgenograms now being obtained is adequate to fulfill the radiologists' need for determining proper beam localization.

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AN AUTOMATIC FIELD MAPPING DEVICE

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KNOWLEDGE of the distribution of intensity across radiation fields is important for radiation therapy machines where a variety of cones, filters, and other beam perturbing devices are employed. Accurate treatment planning requires this information. Also experiments performed with therapy machines usually require knowledge of the intensity distribution.

A device has been constructed which enables the radiologist or physicist to obtain field intensity plots quickly and accurately. Its set-up time is of the order of minutes and much information can be obtained in a relatively short period of time. This is important in busy departments where the radiation equipment is in continuous use.

Essentially the device consists of a detector-probe which is attached to a movable carriage. Any movement of the carriage within the radiation room is translated, by means of selsyn motors, to movement of the chart of an electronic recorder in the control room. The carriage is driven along tracks by a revolving screw driven by a variable speed reversible motor. The detector probe can be either an ionization chamber or a scintillation crystal. The output of the detector is fed into the pen driving circuit of the electronic recorder.

Figure 1 shows the electronic recorder, pen positioning controls and drive motor controls. An actual intensity distribution is visible on the chart. Figure 2 shows the carriage used for scanning and also the detector, in this case a 3 mm. anthracene crystal whose output is being piped to a 1P21 photomultiplier. At this time the field "mapper" was being used to obtain data on the field intensity distributions produced by the Memorial Center telecobalt unit. The detecting circuit is shown schematically in Figure 3. For either ionization

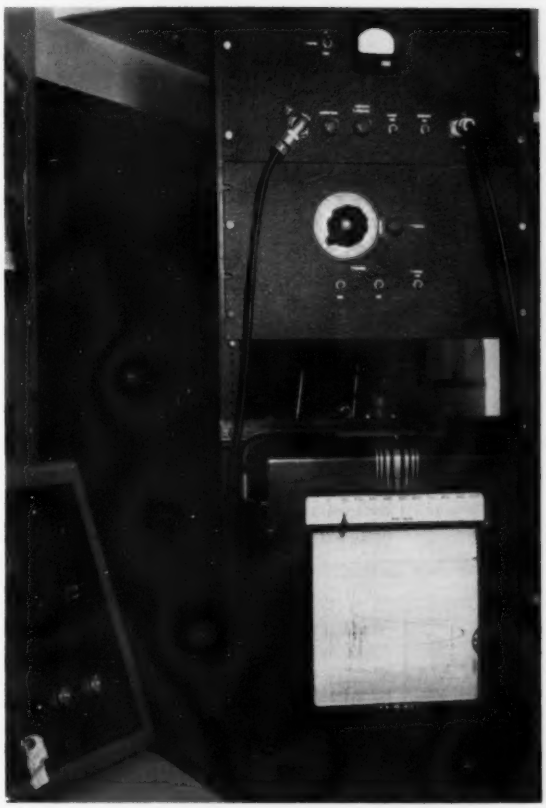

FIG. 1. The electronic recorder, pen positioning controls and drive motor controls.

chamber or scintillation crystal detectors, the input stage consists of a Victoreen 5,800 electrometer tube. With ionization chambers of 1 cm.^{3} volume, 10^9 or 10^{10} ohm input resistors have been found most generally useful. With the 1P28 photomultiplier, used in conjunction with anthracene crystals, a 10^7 ohm input resistor has been satisfactory.

Power for the electrometer tube is obtained from the 220 volt winding of the power transformer of the Brown amplifier. This winding is connected to a rectifier, filter, and regulating stage, and then to a bleeder network from which the prescribed operating voltages are obtained for the

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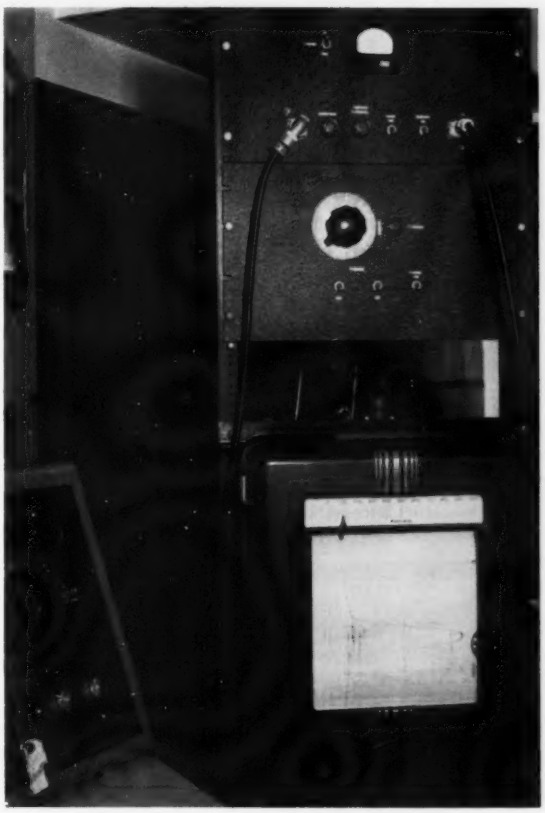

FIG. 1. The electronic recorder, pen positioning controls and drive motor controls.

Power for the electrometer tube is obtained from the 220 volt winding of the power transformer of the Brown amplifier. This winding is connected to a rectifier, filter, and regulating stage, and then to a bleeder network from which the prescribed operating voltages are obtained for the

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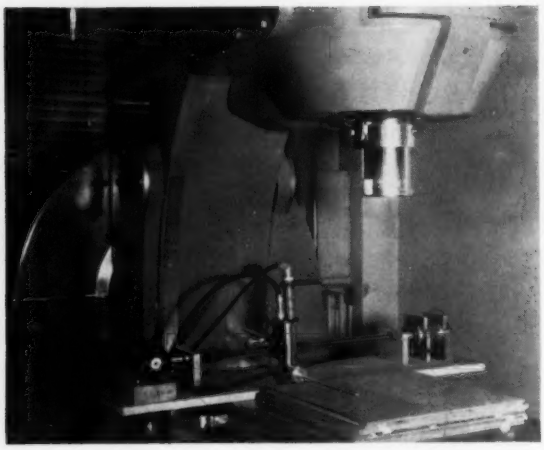

FIG. 2. The scanning carriage with photomultiplier housing and detector probe.

electrometer tube. The current drain from the transformer is approximately 20 milliamperes.

Part of this power is used to supply the reference voltage across the precision balancing potentiometer. Since only positive voltages are available from the regulated supply, a terminal was provided for inserting bucking voltages of either polarity from external voltage sources. This feature permits the apparatus to record positive or negative detector signals and also permits a greater range of voltage to be used than is available from the built-in supply.

The commercially available Brown amplifier is connected between the plate and screen grid of the electrometer tube. Under equilibrium conditions there is no potential difference between these points, the screen grid voltage obtained from the bleeder network being equal and opposite to the voltage drop across the plate load resistor.

The Brown servo-motor in addition to moving the recorder pen and the balancing potentiometer also turns a small Diehl generator which serves to introduce a negative feedback signal which is proportional to the degree of unbalance at the input of the Brown amplifier. This signal (6.5 volts per 1,000 r.p.m.), which can be

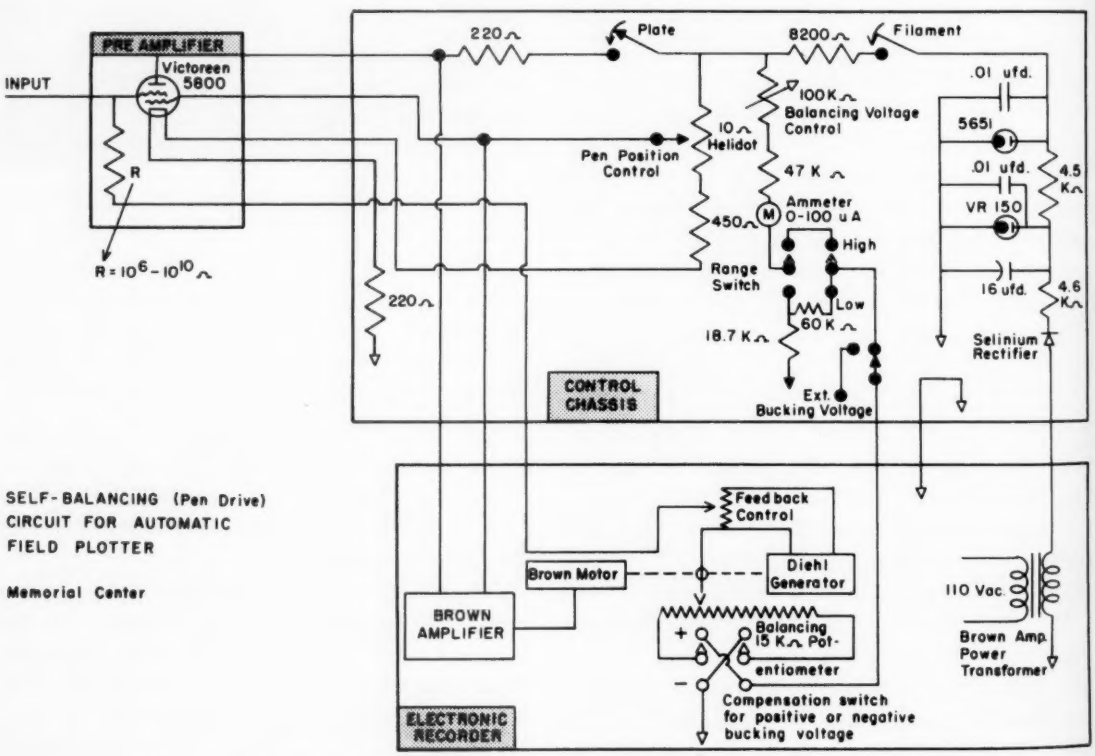

FIG. 3. The self-balancing circuit showing pen positioning and range controls.

attenuated by a potentiometer control, is returned to the input and limits the amount of unbalance which can occur within the system. This is an important feature since large input signals will cause the servo system to overshoot and oscillate about an equilibrium point.

The detector circuit need not be limited to radiation measurements but can be used as a general purpose high impedance recorder. For the work described here an auxiliary master selsyn motor unit was constructed which can accommodate a large range of low or high speed drive motors. In this way chart speeds from one inch per hour to three feet per minute are easily obtained.

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CARCINOMA OF LARYNX*

RESULTS OF ROENTGEN THERAPY DURING A PERIOD OF FIFTEEN YEARS (1937–1952)

By EDWARD L. JENKINSON, M.D., LILLIAN KAO, M.D., PAUL H. HOLINGER, M.D., K. C. JOHNSTON, M.D., *and* R. W. DONNELLY, M.D.

DURING the fifteen year period from 1937 to 1952, a total of 119 cases of carcinoma of the larynx was treated with external roentgen irradiation in the Department of Radiology at St. Luke's Hospital, Chicago, Illinois. All these cases had histologic proof of squamous cell carcinoma before radiation therapy was instituted, except in one instance in which the biopsy showed anaplastic cell carcinoma. Ten patients of this entire group of 119 are not included in the general survey, either because of failure to take more than a few treatments, or due to insufficient data. In the remaining 109 patients, close follow-up examinations were carried out in the Department of Bronchology (Drs. P. H. Holinger and K. C. Johnston) at regular intervals for a varying period up to the present time. Following is a report of the three, five and ten year observation of these 109 patients.

AGE AND SEX

Table 1 shows the age distribution of the patients with the highest incidence apparently in the sixth decade. The average age of the entire group was 59.2 years, the youngest patient being twenty and the oldest eighty-six years of age.

There were 93 males and 16 females, *i.e.*, 85 per cent male and 15 per cent female, giving a ratio of 5.8 to 1 in favor of the male.

RECURRENCES AFTER SURGERY AND PREVIOUS IRRADIATION

Twenty-seven patients in this series had had previous treatment elsewhere for carcinoma of the larynx. Four of these had roentgen therapy and 23 had surgery. All of the 27 had recurrent disease. Sixteen of the 23 surgical cases had total laryngectomies. One had received postoperative irradiation. Four patients had had laryngofissures, and 3 others had various types of local resection. All of these cases are included in our tabulation of survival rate, as will be seen later.

In addition to the above, 3 patients who received initial irradiation in our department underwent laryngectomies later for recurrences. Altogether 30 patients required tracheotomy, 17 prior to, 2 during, and 11 after irradiation. Of these 30 patients, 5 also had gastrostomies, 3 before, 1 during, and 1 after irradiation.

CLASSIFICATION

It is apparent from these studies and those of others that it is not as much the extent or size of the lesion when first seen, as its location that is of prime prognostic value in dealing with carcinoma of the larynx. However, a classification which is based on the extent of the clinical findings is significant. Such a classification, based on the extent of the lesion is as follows (Chart 1):

TABLE I

AGE DISTRIBUTION

Age in Decade	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Average 59.2
Total Number	1	1	15	36	33	18	4	109
Per Cent of Total	0.9	0.9	14.2	33.1	30.1	17.0	3.8	100

* From the Departments of Radiology and Bronchology, St. Luke's Hospital, Chicago, Illinois.

Stage I, lesion involving any one area only;
Stage II, lesion involving any two adjacent areas;
Stage III, lesion involving any two nonadjacent or any three adjacent areas;
Stage IV, lesion involving more than three areas; local or distant metastasis.

Each lesion then must be further classified according to its anatomic site. Those lesions lying within the endolarynx, *i.e.*, between the dotted lines of Chart I, are termed intrinsic, while those arising from or extending to regions outside the dotted lines are called extrinsic.

A difference of opinion in regard to a definition of the terms intrinsic laryngeal cancer and extrinsic laryngeal cancer often arises. The delineations indicated in Chart I, followed throughout this presentation are those suggested and generally used by the radiologists (Drs. E. L. Jenkinson and Lillian Kao). From the laryngologic point of view (Drs. P. H. Holinger and K. C. Johnston), intrinsic and extrinsic differentiation is made on the basis of the pattern of the lymphatics of the larynx, *i.e.*, only lesions involving the true cords alone are considered intrinsic, all others being considered extrinsic. This is because of the fact that the lymphatics are almost nonexistent in the true cords, but rich in their distribution throughout the remainder of the larynx. Thus, a classification on a more consistent anatomic and clinical basis is possible.

CHART I

ANATOMIC CLASSIFICATION OF CANCER OF THE LARYNX FOR USE IN RADIATION THERAPY

RIGHT		LEFT
Pyriform Sinus		Pyriform Sinus
Aryepiglottic Fold	Epiglottis	Aryepiglottic Fold
Extrinsic		Extrinsic
Intrinsic		Intrinsic
False Cord		False Cord
	anterior	
Ventricle		Ventricle
	commissure	
True Cord		True Cord
Intrinsic		Intrinsic
Extrinsic	Thyroid	Extrinsic
	Cricoid	

TABLE II

CLASSIFICATION ACCORDING TO CLINICAL STAGES

Stage	Extrinsic	Intrinsic	Total Number	Percentage of Total
I	5	11	16	14.7
II	4	2	6	5.5
III	7	12	19	17.4
IV	59	9	68	62.4
Total	75	34	109	100.0

An additional point of differentiation is the motility or lack of motility of the involved vocal cord. This is most significant in the evaluation of the prognosis and the choice of therapy of the early lesion, Stage I, intrinsic.

The distribution of the 109 patients in this series according to the classification given in Chart I is shown in Table II.

It is easily seen that the majority of our patients, 62.4 per cent were far-advanced cases. These include the 27 patients who had previous surgery or roentgen therapy. Forty-five of these far-advanced cases had lymph node metastases when first seen. Only one-fifth of the entire series were seen in earlier stages, *i.e.*, Stages I and II. Extrinsic lesions were more than twice as numerous as intrinsic ones.

The relative frequency of the various anatomic structures as point of origin of the lesion is listed in Table III without regard to the extension of the lesion. This was determinable only in 72 of the 109 cases.

RESULTS

Following Martin's "Method of Reporting End Results," we include each and every case that was referred for treatment regardless of previous treatment or the fact that the patient was in an obviously termi-

Table III

BREAK-DOWN OF LESIONS ACCORDING TO SITE OF ORIGIN

Origin	Total Number	Percentage of Total
True Cord	37	51.4
Epiglottis	13	18.1
Pyriform Sinus	9	12.5
Post-cricoid	5	6.9
Arytenoid	3	4.2
Aryepiglottic Fold	2	2.8
False Cord	2	2.8
Anterior Commissure	1	1.3
Total	72	100.0

nal stage. Twenty cases of the entire group of 109 were considered indeterminate for the following reasons: Thirteen died of other causes without evidence of laryngeal lesion in less than five years; 7 were lost to follow-up. Of the 89 determinate cases, there are 30 survivals, 16 of which are alive three to four years, 12 for five to nine years, and 2 for more than ten years. Only the relative cure-rates, *i.e.*, cure-rate per observed case, are calculated as these are more accurate than the absolute cure-rate.

Table IV shows an over-all cure-rate of 33.7 per cent. This figure is obtained from an entirely unselected group of patients, the majority of whom were in a far-advanced stage of the disease. We also see that a high cure-rate of 78.4 per cent in Stage I dwindles down to a mere 18.5 per cent in Stage IV. Thus, the importance of early diagnosis is self-evident.

In Table V the intrinsic lesions are seen to carry a survival rate of 60.7 per cent as against 21.3 per cent of the extrinsic group.

Table V

CURE-RATES IN TERMS OF ANATOMIC CLASSIFICATION

	Intrinsic	Extrinsic
Total Number	34	75
Indeterminate Cases	6	14
Determinate Cases	28	61
Failures	11	48
Successes	17	13
Cure-rate	60.7%	21.3%

Table IV

RESULTS OF ROENTGEN THERAPY (1937–1952)

All Cases	Total	Clinical Stages			
		I	II	III	IV
	109	16	6	19	68
Indeterminate Cases	20	2	2	2	14
Dead without disease in less than 5 years	13	1	1	2	9
Lost to follow-up	7	1	1	0	5
Determinate Cases	89	14	4	17	54
Failures	59	3	2	10	44
Dead with disease	54	2	2	8	42
Alive with disease	5	1	0	2	2
Successes	30	11	2	7	10
Relative Cure-rate	33.7%	78.4%	50%	41.2%	18.5%
Absolute Cure-rate	27.5%				

Table VI

RESULTS IN TERMS OF CLINICAL STAGES AND ANATOMIC SITES (DETERMINATE GROUP)

Stage	I		II		III		IV	
Site	Intrinsic	Extrinsic	Intrinsic	Extrinsic	Intrinsic	Extrinsic	Intrinsic	Extrinsic
Number of Patients	10	4	0	4	10	7	8	46
Failures	1	2		2	5	5	5	39
Dead with disease	0	2		2	4	4	5	37
Alive with disease	1	0		0	1	1	0	2
Successes	9	2		2	5	2	3	7
Cure-rate	90.0%	50%	0	50%	50%	28.6%	37.5%	15.2%
Average Cure-rate	78.4%		50%		41.2%		18.5%	

That this difference is due at least partly, to the extent of the lesion is readily seen in Table VI. Here the survival rates are further correlated with the anatomic classification in terms of extrinsic and intrinsic location. From this we note that the intrinsic lesions are seen much more often than the extrinsic ones in Stages I and II while the reverse is true in Stages III and IV.

Our results are in accordance with the known fact that intrinsic lesions are more curable than the extrinsic ones, and therefore, the question arises: Is this primarily due to the anatomic location or the extent and size of the lesion? To the laryngologist, naturally, the intrinsic lesions would be more curable than the extrinsic ones when surgery is considered. As radiologists, however, we feel that since these lesions are of the same histologic structure and are equally accessible to external irradiation regardless of their location inside or outside of the endolarynx, the size and extent of the lesion should be the most important factor in evaluating the results of treatment. As a rule, extrinsic lesions are more difficult to judge clinically as to their exact extent. Thus, errors in staging often occur when a lesion is only partially seen. Until we have a sufficient number of patients in both groups with lesions of comparable sizes, as judged by experienced laryngologists, it will be hard to draw a conclusion as to whether intrinsic lesions are more curable because of their location or because of their earlier discovery, as far as roentgen therapy is concerned.

With respect to the site of origin of the lesion, the survival rates are seen to be highest in cordal lesions (Table VII). This is in agreement with reports from other clinics. A lesion on the anterior two-thirds of the true cord with unimpaired mobility carries an excellent prognosis. In our series we have a survival rate of 90 per cent in Stage I, intrinsic lesions (Table VI).

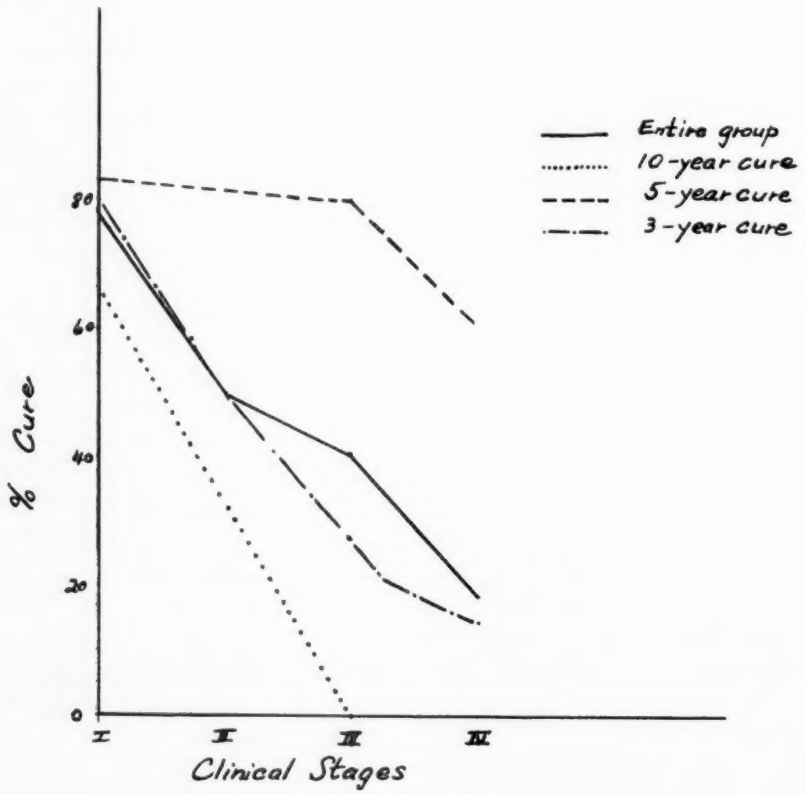
In Table VII are shown the results in terms of the site of origin of the lesion. Included in this table were also those patients who had extensive disease and those who had previous treatment. Of the 23 with extensive disease, 2 are alive and well, giving a cure-rate of 8.7 per cent. As pointed out earlier in this report, 27 patients were previous surgical or radiation failures. Of the 9 post-surgical patients who were followed for a sufficient period, 7 are dead and 2 are alive and well. One of the living had a partial epiglottectomy with neck dissection and the other had a laryngofissure for a small cordal lesion before recurrences developed. Of the 3 patients who had laryngectomy following irradiation in our

TABLE VII

RESULTS IN TERMS OF SITE OF ORIGIN OF THE LESION

Site of Origin	Number Observed	Living	Dead or with Disease	Cure-rate
True Cord	28	16	12	57.1%
Epiglottis	10	3	7	30%
Post-cricoid	5	2	3	40%
Pyriform Sinus	4	2	2	50%
Arytenoid	4	1	3	25%
False Cord	2	1	1	50.0%
Anterior Commissure	1	1	0	100.0%
Extensive	23	2	21	8.7%
Post-radiation	3	0	3	0
Post-surgical	9	2	7	22.2%
Lymph Node Metastases	32	5	27	15.6%

department, 2 are dead and 1 still alive but with disease. None of the 3 patients treated for recurrences after previous roentgen therapy survived. Likewise, all 6 patients who had received additional courses of radiation for recurrences in our own department are either dead or still have the disease. As regards the 32 of the 45 patients with lymph node metastases who were followed, 5 are alive and 27 are dead.



GRAPH 1. Survival curves in different stages for the three, five, and ten year cures and the entire group.

Graph 1 shows the survival curves per stage for the three, five, and ten year curves and the entire group.

TECHNIQUE AND REACTIONS

The technique used was similar in the majority of the patients with only little variations over the years. The factors employed were: 200 kv. constant potential, 10 ma., Thoreus II filter (half-value layer of 2 mm. Cu), 60 cm. target-skin distance and 8.0 cm. circular cone. Two opposing lateral ports were used. Each port was treated with a daily dose of 140 r in air over ten minutes until a total dose of 3,780 r (air) was given per port. This took a period of four to five weeks. In an average neck with a lateral diameter of 11 cm., the minimum depth dose at 5.5 cm. was 4,700 r. The skin dose in each area was approximately 5,500 r. Localization films with lead markers over the center of each field were taken with the actual treatment beam at the start of each series. For lesions in the earlier stages, a 5.0 cm. cone was used, instead of 8.0 cm. cone. In the years before 1945, larger fields of 10 cm. in diameter were employed. With the exception of 2, all patients were able to complete the prescribed series of treatments. In the 2, who nearly but not quite finished the series, the irradiation was interrupted because of severe skin reaction and pain. A moist desquamation of the skin was noted in the majority of the patients in the fourth week, but adequate healing invariably took place within two months after the completion of treatment. As mentioned earlier, 2 patients required emergency tracheotomy during the irradiation, and 11 more after irradiation, due to edema. Telangiectasia was observed in 4 patients years following treatment, but radiation necrosis was not proved in any case. In some patients, after the control of the disease, hoarseness persisted for many years. This may be due to post-radiation fibrosis and edema. Unfortunately, the exact incidence of this sequela cannot be ascertained from our file.

CONCLUSION

1. The over-all cure-rate of 33.7 per cent in this consecutive series of 109 patients with carcinoma of the larynx parallels the results from other clinics in unselected groups of cases. Considering the fact that 62.4 per cent of our patients were treated in a far-advanced stage of the disease, we believe this figure of a 33.7 per cent cure-rate represents the optimum result that can be achieved with present-day radiation technique.

2. It is the size and extent of the lesion when first seen, in addition to its location, which is of prime prognostic significance in dealing with carcinoma of the larynx.

3. The intrinsic lesions are usually seen in earlier stages and are more easily evaluated as to their size and extent. It takes an experienced laryngologist to accurately examine the patient so that staging of the disease may be correct.

4. Early intrinsic lesions of the larynx confined to the cords are best treated by irradiation. The importance of early diagnosis is indicated by the high cure-rate of 78.4 per cent in Stage I as against 18.5 per cent in Stage IV.

5. Roentgen therapy given after previous irradiation failures in carcinoma of the larynx had not proved to be successful; however, a 22.2 per cent cure-rate was obtained in recurrences after previous surgery.

6. While the survival rate achieved by roentgen therapy in advanced cases of carcinoma of the larynx is extremely low, higher survivals have not been reported from surgical treatment alone. It is possible that a revision and combination of both surgical and radiation techniques may bring about a more satisfactory result in these cases.

7. Close cooperation between the laryngologist and the radiologist is essential in the management of patients with carcinoma of the larynx. Preferably a standardized classification should be devised that could be adopted universally, such as that in carcinoma of the uterine cervix, so

that results from different places may be compared and more accurately evaluated.

SUMMARY

1. The results of roentgen therapy over a fifteen year period (1937 to 1952 inclusive) in an unselected group of 109 patients with carcinoma of the larynx are reported with detailed analysis of the survival rates.

2. The importance of early diagnosis is emphasized by the good response of these cases to treatment.

3. The cure-rate in patients with extensive carcinoma of the larynx remains low. The authors believe that a combination of both surgery and radiation therapy may achieve a more satisfactory result in these cases.

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SQUAMOUS CELL CARCINOMA OF THE THORACIC ESOPHAGUS

AN EVALUATION OF TREATMENT METHODS*

By HARRY W. BURNETT, JR., M.D., *and* S. W. MOORE, M.D.

NEW YORK, NEW YORK

BY WHAT therapeutic measures can the majority of patients with such a lesion be provided with the maximum amount of survival or palliation? In an effort to appraise this question all cases with the histologically proved diagnosis of squamous cell carcinoma of the thoracic esophagus seen in the clinics of The New York Hospital from 1940 through 1950 have been included for evaluation.

The ideal treatment would be one which could be successfully used for all patients with a minimum of morbidity and mortality. Consequently, from the standpoint of the patient, if a method of treatment is too formidable to tolerate or survive, the method itself must be considered a failure. Statistically, such a fundamental approach regarding the welfare of the patient requires that all patients be included for analysis, and not merely an academically selected few who survive after a specific procedure.

In excellent recent reviews of this subject it has been stated that three year survivals of 33 per cent[5] to 39 per cent[12] are obtainable by resection and anastomosis. It should be emphasized that these figures are based upon a selected group of patients only; namely, those having a resection and not dying in the hospital postoperatively. Such figures, naturally, portray an artificial and not an absolute picture of the total problem.

By employing the same method of calculation the present series would result in a three year survival rate of 50 per cent (3 alive three years later of 6 patients surviving resection), whereas the absolute salvage rate by surgery (resection) actually would be 5.5 per cent (3 alive three years later of 54 candidates for cure).

The purpose of this study is to present an evaluation of the various methods of treatment employed regarding: (1) applicability, (2) mortality, (3) value in prolonging or palliating the patient's life.

MATERIAL STUDIED

Only histologically proved squamous cell carcinomas of the thoracic esophagus have been included since they are the most common type, and many of the adenocarcinomas have been regarded as being of gastric origin. Squamous celll carcinoma is also much more responsive to irradiation than adenocarcinoma, which therapeutically is an entirely different condition.

Of a total of 64 patients so diagnosed, 10 had conclusive evidence of distant metastases upon admission, with an average survival of 3.6 months. The remaining 54 patients have been considered as candidates for possible "cure," and represent the material studied in detail.

Table 1 gives a tabulation of the general status of the patient material.

COURSE AND FOLLOW-UP

All patients were admitted to the surgical service for diagnostic procedures and surgical treatment. Figure 1 illustrates the disposition and follow-up of the patients. Fifty-four patients had no demonstrable evidence of distant metastases and were considered as suitable candidates for curative surgery, *i.e.*, resection and anastomosis.

As will be noted, 39 of the 54 (72.2 per cent) had a thoracotomy performed for

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TABLE I

SQUAMOUS CARCINOMA OF THE THORACIC ESOPHAGUS
GENERAL STATUS OF PATIENT MATERIAL

Age: 63.2 years average. Range: 43 to 92 years
Sex: male; 46 patients (85.2%), female; 8 patients (14.8%)
Duration of Symptoms: predominantly dysphagia; 2.98 months average
Level of Lesion: upper third, 9 patients, 16.6%
middle-third, 28 patients, 51.8%
lower third, 17 patients, 31.4%

evaluation of the possibility of a resection. Thirteen were considered poor surgical risks, and 2 refused operation. Of the thoracotomy group, 17 (31.4 per cent of the original 54, and 43.6 per cent of the 39 thoracotomies) had a resection completed and 22 were closed after exploration revealed a resection was not feasible. Of the 17 resected, 7 died in the hospital, giving a mortality of 41.2 per cent. Two of the 22 which were explored and not resected likewise died in the hospital, a mortality of 9.1 per cent.

Of the 17 resected patients, 4 were referred for roentgen therapy because residual tumor was known to be present. This leaves 6 patients treated entirely by surgery with a possibility of being cured (15.4 per cent of 39 thoractomies, and 11.1 per cent of the original 54 patients).

The number of survivors by months (from the date of proved diagnosis) is illustrated in Figure 1. The chart is completed up to 36 months. It should be pointed out that

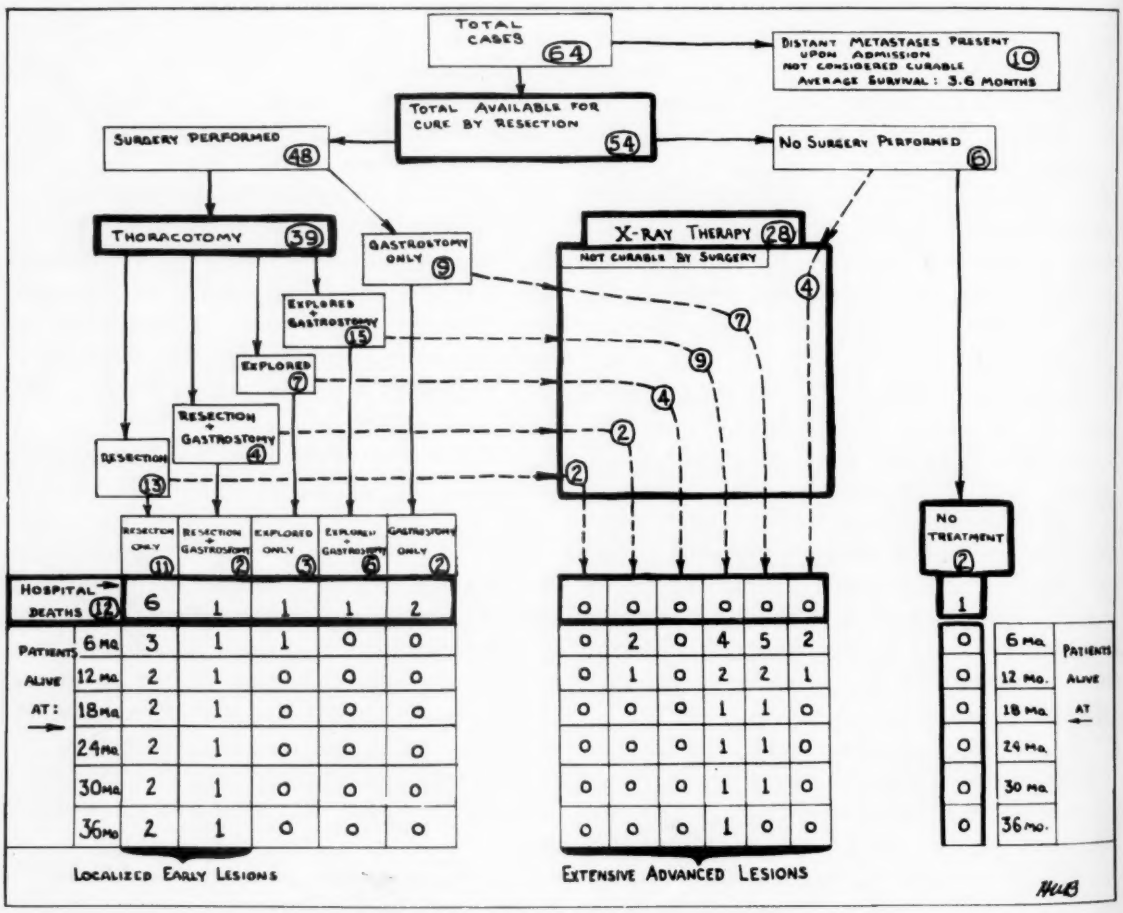

TOTAL CASES 64
DISTANT METASTASES PRESENT UPON ADMISSION NOT CONSIDERED CURABLE AVERAGE SURVIVAL: 3.6 MONTHS 10
TOTAL AVAILABLE FOR CURE BY RESECTION 54
SURGERY PERFORMED 48
NO SURGERY PERFORMED 6
THORACOTOMY 39
GASTROSTOMY ONLY 9
X-RAY THERAPY 28
NOT CURABLE BY SURGERY
EXPLORED + GASTROSTOMY 15
EXPLORED 7
RESECTION + GASTROSTOMY 4
RESECTION 13
NO TREATMENT 2
RESECTION ONLY 11
RESECTION + GASTROSTOMY 2
EXPLORED ONLY 3
EXPLORED + GASTROSTOMY 6
GASTROSTOMY ONLY 2
HOSPITAL DEATHS 12
6 1 1 1 2
PATIENTS ALIVE AT:
6 MO. 3 1 1 0 0
12 MO. 2 1 0 0 0
18 MO. 2 1 0 0 0
24 MO. 2 1 0 0 0
30 MO. 2 1 0 0 0
36 MO. 2 1 0 0 0
0 0 0 0 0 0
0 2 0 4 5 2
0 1 0 2 2 1
0 0 0 1 1 0
0 0 0 1 1 0
0 0 0 1 0 0
1
0 6 MO.
0 12 MO.
0 18 MO.
0 24 MO.
0 30 MO.
0 36 MO.
PATIENTS ALIVE AT
LOCALIZED EARLY LESIONS
EXTENSIVE ADVANCED LESIONS

FIG. 1. Squamous cell carcinoma of the thoracic esophagus. Treatment, disposition and follow-up of all patients.

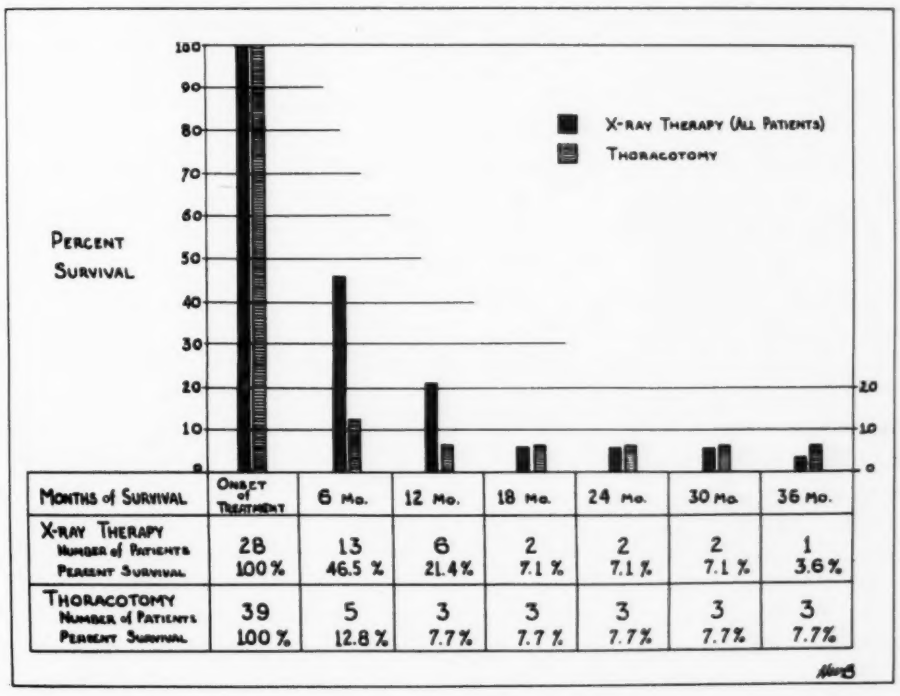
of the resected group, 1 patient survived until 51 months, while another is still alive at 51 months.

Of the original 54 patients, 28 (51.8 per cent) who were found to be unsuitable for operation or an adequate resection were referred for roentgen therapy. The follow-up is shown in Figure 1. Although these patients were in an advanced stage of the disease, none died as a hospital mortality, and 13 (46.4 per cent of the 28) were still alive with a functioning esophagus six months later. Of long term follow-ups, 1 patient survived 35 months, another 38 months. The complication of esophageal perforation was not found in any of the treated patients.

What was the surgical salvage rate in the 39 patients subjected to exploratory thoracotomy as compared with the group of surgically incurable patients referred for roentgen therapy? Figure 2 illustrates the percentage survival by months. Although few long term survivals were obtained by either method, surgery resulted in a far lower percentage survival during the first year as a result of the high operative mortality. It should also be emphasized that the thoracotomy figures represent only 39 of the 54 candidates for thoracotomy, since 15 patients have been omitted from analysis because they were found unsuitable to undergo the operation.

SURGICAL TREATMENT

Torek,[14] in 1913, first successfully resected the esophagus for carcinoma. This was a tremendous advance. In 1938, Adams and Phemister[1] reported the first successful resection and esophagogastrostomy. In 1947, this patient was reported by Phemister as being well, nine and one-half years after operation. From then on there was an increased interest in the surgical treatment of carcinoma of the esophagus and with better anesthesia, greater availability of antibiotics and more liberal use of blood, large series of cases have been reported. As the operator's experience increased, his mortality rate became re-



MONTHS of SURVIVAL	ONSET of TREATMENT	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.
X-RAY THERAPY NUMBER of PATIENTS	28	13	6	2	2	2	1
X-RAY THERAPY PERCENT SURVIVAL	100%	46.5%	21.4%	7.1%	7.1%	7.1%	3.6%
THORACOTOMY NUMBER of PATIENTS	39	5	3	3	3	3	3
THORACOTOMY PERCENT SURVIVAL	100%	12.8%	7.7%	7.7%	7.7%	7.7%	7.7%

FIG. 2. Squamous cell carcinoma of the thoracic esophagus. Follow-up of patients subjected to thoracotomy as compared with all patients having roentgen therapy.

duced. However even so, when the total cases seen are balanced against three-year survivals, the outlook remains poor.

Although Sweet[12,13] does not give the total cases seen, he reports that 39.1 per cent of those resected and surviving the operation have lived three or more years. Gibbon and co-workers[5] in 63 patients with squamous cell carcinoma of the esophagus, have 1 patient who has survived 36 months. As this was 1 of 3 patients operated three years previously, it can be converted, as Sweet does, to 33.3 per cent three-year survival. Parker, *et al.*[9] in 170 cases with primary epidermoid carcinoma, have 2 patients with no evidence of carcinoma, 1 at 10 months and the other at 36 months.

Merendino and Mark,[8] based on a series of 100 cases of squamous cell carcinoma of the esophagus, conclude that 34 per cent have a localized curable disease. The esophagus presents symptoms early, and delay in detecting carcinoma is due to difficulty in establishing a diagnosis. Yet, despite early diagnosis, radical excision is often impossible since the esophagus occupies a very small space and is in intimate contact with many vital structures, such as the hili of the lungs, the aorta and the heart. Only at the lower portion is it possible to include adequate removal of the diaphragm and stomach with the adjacent lymph drainage. Although the mortality rates in resecting the mid esophagus and lower esophagus are similar, the chances of cure in the lower one-third are much better.

Ravitch, *et al.*[10] in a paper given at a meeting of The American Thoracic Society in 1952 expressed pessimism about the treatment and cure of carcinoma of the esophagus by surgery.

In the present series of 54 cases, 48 were operated upon, 39 had a thoracotomy, 17 were resected, and 8 had a gastrostomy only (Fig. 1). Of those resected, 7 died in the hospital, a mortality rate of 41.2 per cent. (In more recent work the mortality rate has been reduced to approximately 25 per cent.) Four had a palliative resection, 13 had apparently complete removal of the tumor and were then considered as theoretically cured.

Although this picture is grim there remains hope. From the surgical viewpoint it is felt that the only way to cure patients with carcinoma of the esophagus is by radical excision of the tumor, as done in other locations of the body.

ROENTGEN THERAPY

From the literature there is ample evidence of the ability of roentgen therapy to control squamous cell carcinoma of the esophagus. A patient has been reported by Jacobsson[7] free from evidence of disease six years after treatment. Watson and Brown[15] in a series of 12 cases had 5 patients living free of disease for periods up to fifty-two months. Of 4 patients who were autopsied none showed microscopic residual cancer in the treated areas. Freid[3] described a case living seven years and seven months. This same patient remains alive thirteen years after treatment.[4] Strandquist[11] in a series of 36 patients reported 4 surviving over two years. Of 5 treated by Buschke and Cantril,[2] 1 was alive without evidence of recurrence three and one-half years after treatment.

Dosage requirements from the various references indicate that it is necessary to deliver from 5,000 to 6,000 r tumor dose within a period of four to six weeks. Inadequate irradiation, like inadequate surgery, cannot be expected to produce long term survivals. The data of Holmes and Schulz[6] employing supervoltage therapy has often been referred to[12,13] as showing irradiation to be of little value. This is no longer justifiable since the maximum tumor dose in their series was 3,000 r, which is approximately one-half of the amount known to be necessary for carcinocidal effects in esophageal tumors.

In the present series, 28 patients were referred for roentgen therapy after it became evident that an adequate resection would not be feasible; the disease, therefore, was far-advanced and surgically incurable. They were treated with conventional 250

kv. equipment, with quality ranging from half-value layer of 1.0 to 2.6 mm. of copper, at 50 cm. or 70 cm. target skin distance. Portals were usually three anterior and three posterior, with the central rays converging at the tumor site.

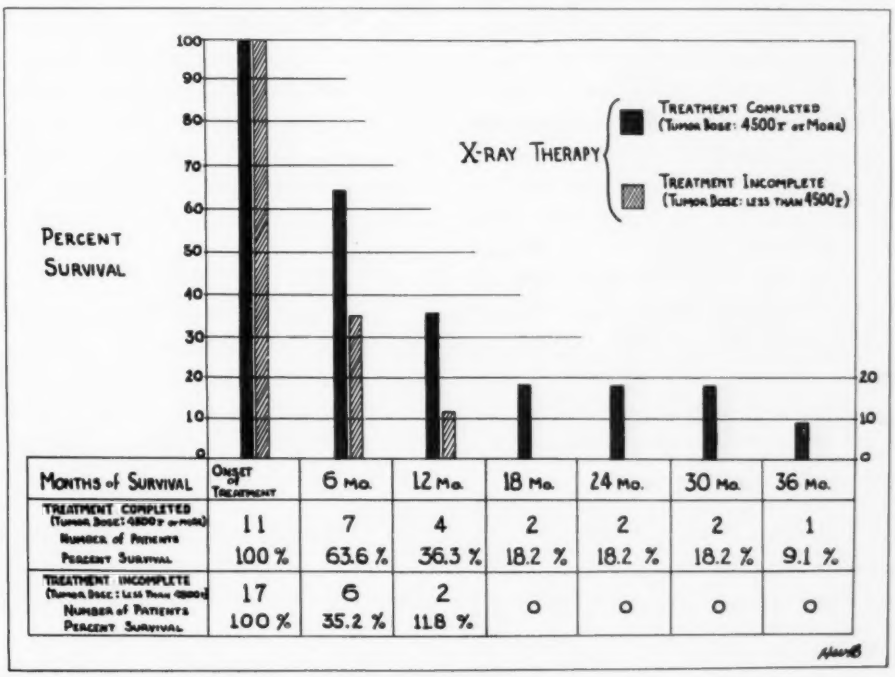
Although a carcinocidal tumor dose was recognized as necessary, it was seldom possible to deliver it for reasons to be discussed further in this paper. Of the 28 patients referred for irradiation, 17 (60.7 per cent) received what may be considered as an incomplete course of treatments, namely a tumor dose of less than 4,500 r. The average duration of survival of this group was 5.2 months. Those who completed a course of treatments had a much better opportunity for survival, as shown in Figure 3.

Why is it that so few of the patients completed an adequate series of treatments? It is of particular importance to consider this question since long term survivals can be obtained if patients are treated adequately.

Twenty-four of the 28 (86 per cent) were postoperative patients; the others were not considered suitable candidates for an operation. Seventeen (61 per cent) were post-thoracotomy and were found to have disease too extensive for a satisfactory resection.

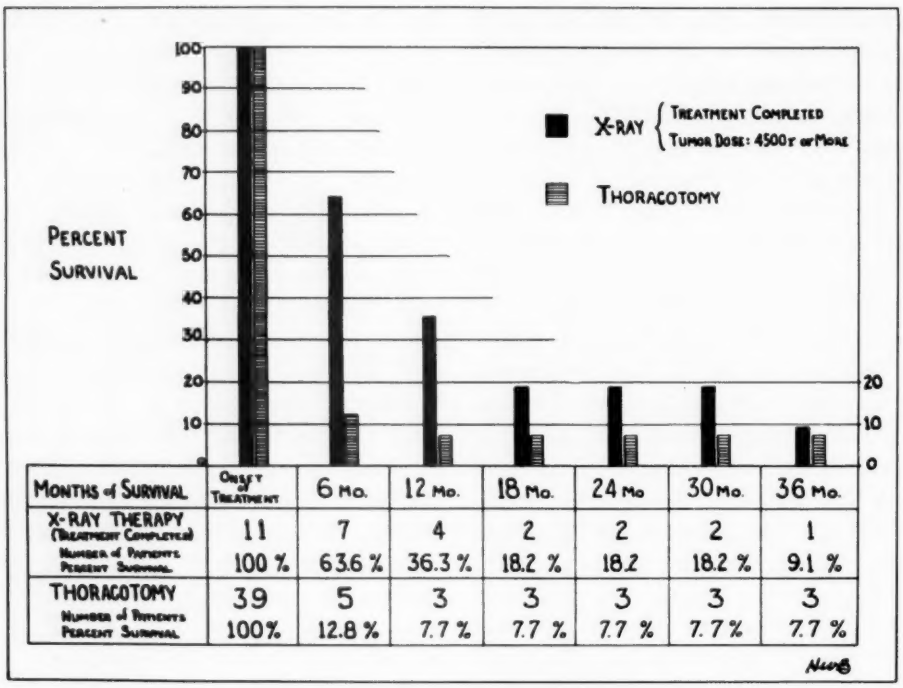
Although an adequate series of treatments usually requires thirty-five to forty days, these postoperative, debilitated patients with an average age of sixty-three years received treatments while hospitalized for an average of 11.6 days. The remaining three to four weeks of treatments were to be attempted on an ambulatory out-patient basis. In most instances this proved unfeasible accounting for the failure of the patient to complete the course of treatments. In other cases, treatments were terminated by the referring physician because of the prevailing belief that they would be of no significant value.

The preceding material provides a basis for suggesting ways to improve end-results. Surgery (resection) in this series showed a high mortality rate (41.2 per cent of resections). The irradiated group had no



MONTHS of SURVIVAL	ONSET OF TREATMENT	6 MO.	12 MO.	18 MO.	24 MO.	30 MO.	36 MO.
TREATMENT COMPLETED (TUMOR DOSE: 4500 r OR MORE)							
NUMBER of PATIENTS	11	7	4	2	2	2	1
PERCENT SURVIVAL	100 %	63.6 %	36.3 %	18.2 %	18.2 %	18.2 %	9.1 %
TREATMENT INCOMPLETE (TUMOR DOSE: LESS THAN 4500 r)							
NUMBER of PATIENTS	17	6	2	0	0	0	0
PERCENT SURVIVAL	100 %	35.2 %	11.8 %				

FIG. 3. Squamous cell carcinoma of the thoracic esophagus. Follow-up of patients receiving roentgen therapy with comparison of those who completed treatments and those whose treatments were incomplete.



MONTHS of SURVIVAL	ONSET of TREATMENT	6 Mo.	12 Mo.	18 Mo.	24 Mo	30 Mo.	36 Mo.
X-RAY THERAPY (TREATMENT COMPLETED) NUMBER of PATIENTS	11	7	4	2	2	2	1
PERCENT SURVIVAL	100 %	63.6 %	36.3 %	18.2 %	18.2	18.2 %	9.1 %
THORACOTOMY NUMBER of PATIENTS	39	5	3	3	3	3	3
PERCENT SURVIVAL	100%	12.8 %	7.7 %	7.7 %	7.7 %	7.7%	7.7 %

FIG. 4. Squamous cell carcinoma of the thoracic esophagus. Follow-up of patients subjected to thoracotomy as compared with those who completed a course of roentgen treatments.

mortality which could be directly attributed to the method. The irradiated group of advanced unresectable lesions when compared with the operative group demonstrated a significantly higher percentage survival during the first year and a comparable salvage rate at two years, although a lower figure at three years (See Fig. 2).

Figure 4 provides a comparison of the percentage survival of patients who had completed a course of roentgen treatments (tumor dose of 4,500 r or more) as compared to the group having a thoracotomy without irradiation. Inasmuch as the irradiated group comprised only far advanced unresectable material it is evident that better results could be anticipated if early small lesions were also included.

From the viewpoint of the radiologist, it is believed that the over-all survival and palliation rate could be much improved if patients with squamous cell carcinoma of the esophagus were treated primarily by adequate irradiation without preliminary thoracotomy. Experience has shown that adequate treatment can be accomplished if patients are hospitalized and receive nutritional and other supportive measures for the duration of the treatments.

Even though technical advances such as rotational and supervoltage therapy are known to be of further value, early prompt treatment with hospitalization of the patient are still of basic importance if patients are to receive the full benefit of available equipment and methods.

SUMMARY

1. A study has been done of patients with squamous cell carcinoma of the thoracic esophagus in an effort to evaluate methods of treatment; namely, surgical resection and roentgen therapy with particular regard to applicability, mortality, and end-results.

2. The material (64 patients) represents all histologically proved cases seen in the clinics of The New York Hospital from 1940 through 1950.

3. Follow-up data have been obtained on all patients and have been compiled at six month intervals up to three years.

4. The problem has been discussed from both the surgical and radiotherapeutic viewpoints by considering reports in the literature and the findings in the present series, and by suggesting proposals for improving end-results.

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SOME BASIC CONCEPTS REGARDING TUMORS OF LYMPHOID TISSUE*

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IT IS axiomatic that the classification, histogenetic interpretation, and clinicopathologic interrelationships of the malignant lymphomas should be predicated on the application of sound biologic principles. Too often, these principles have been ignored or forgotten, and, as a result, chaos in nomenclature, concepts and precepts has been inevitable. The concepts to be discussed are neither new, unique, nor profound. They are germane and applicable to virtually all mammalian tissues and to the host of neoplasms originating from them. As a relevant example, let us consider some of these principles as they apply to the reticuloendothelial system.

Of fundamental importance is the pluripotential nature of the primitive reticuloendothelial cell with its propensity for biologic and histologic transformations. Both the functions of this cell and its derivatives, such as phagocytosis, antibody production, formation and destruction of blood cells, and the multiplicity of cell types involved in these functions indicate the pluripotentialities of these cells. The clinical as well as histologic variations encountered in reactions of the reticuloendothelial system to injury are manifold. The nonspecific hyperplasias resulting from a variety of infections, the granulomatous diseases, the numerous diseases associated with hematopoiesis or lack thereof, the so-called "storage" diseases and the pseudoneoplastic proliferative reactions, such as are observed in eosinophilic granuloma of bone, Hand-Schüller-Christian disease and the like, are all indications of the extraordinary capacity of the reticuloendothelial system to react in a variety of ways. It is small wonder then that neoplasms of reticuloendothelial origin should exhibit such a galaxy of cellular combinations and transformations which so often profoundly influence or determine the clinical course.

Equally significant are the concepts of cellular differentiation, maturation, and biologic history of cells. There are two great classes of cells, the so-called intermitotics and the postmitotics. Only the former need concern us here. The vegetative intermitotics, of which primitive reticuloendothelial cells are examples, serve as reservoirs for new cellular life. These divide into daughter cells, one group of which remains perpetually young and undifferentiated, never taking part in development or maturation, but dividing repeatedly into daughter cells just as immature as their parents. The other group, the differentiating intermitotics, divides to form cells with greater degrees of differentiation. Additional divisions result in further differentiation and maturation. It is in this maturation cycle that the leukopoietic cells develop from the primitive reticuloendothelial cells, the parents of all blood cells, through the blast stages, ultimately to evolve into mature white blood cells. Many mitotic divisions and stages of development are encountered in this cycle before a mature white cell is evolved. Fortunately, names have not been given to all of these stages, and in many instances, the cells vary only slightly in their histologic appearance as they progressively, and almost imperceptibly, merge from one stage to another.

Relevant to this concept also, is the fact that *mature* white blood cells are incapable of mitotic division. Therefore, dedifferentiation, anaplasia, or reversion to an embryonic state is impossible. What then is the mechanism by which normal leuko-

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poietic tissue is converted into neoplastic tissue? At any immature stage or at several different stages of the maturation cycle, an *arrest in differentiation* may occur. The cause of this arrest is unknown. The arrested cells may continue to divide at a normal rate or may proliferate at an increased rate. In any event, the number of intermitotic or immature cells will increase rapidly, while the number of mature cells will decrease correspondingly. Since the differential bone marrow count and that of the peripheral blood in normal individuals is more or less constant, in the final analysis, this constancy can only be maintained when one of a pair of recently divided cells remains behind as an intermitotic form to divide again, while the other matures to supply additional replacements for the colony of functioning cells.

Recognition and understanding of these principles provide the insight necessary to evaluate the biologic activity of the lymphomas. The several subdivisions of malignant lymphoma are not distinct entities, but related variants of a single neoplasm. Virtually all of the lymphomas, irrespective of type, are mixed, even though they are predominantly of one type or another. To be otherwise would be biologically impossible in view of the concepts of differentiation and maturation. The merging of Hodgkin's disease with reticulum cell sarcoma on the one hand and with lymphocytic lymphoma on the other, for example, is not an exceptional phenomenon. This mutability applies equally well to other diseases involving the reticuloendothelial system; histologic as well as clinical components of eosinophilic granuloma of bone, Hand-Schüller-Christian disease and Letterer-Siwe disease may be manifest in the same individual. Neither is it especially remarkable that in approximately 25 per cent of all the malignant lymphomas, metamorphosis from one type of lymphoma to another, usually from a well differentiated to a less well differentiated type, occurs. Again, the clinical manifestations tend to parallel the change in histologic components. Such a transformation may occur after a few weeks or after several years. It is not uncommon, for example, for a giant follicular lymphoma to change to a reticulum cell sarcoma with concomitant alteration in the clinical course from an insidious, relatively slow to a rapidly progressive one. Lastly, in this regard, it is not unusual to encounter in a given patient one type of lymphoma in one area, and another type in still a different area. When such variations occur, the pathologist often is accused of having rendered an erroneous diagnosis, when in actuality, such variations are inherent in the biologic nature of the lymphomas. These mutations, furthermore, are not peculiar to neoplasms of the reticuloendothelial system, but are ecumenical in a wide variety of neoplasms. It is customary, for example, to observe chondrosarcomatous, fibrosarcomatous, and even hemangiosarcomatous areas in a primary osteogenic sarcoma or in its metastases. Basically, the tumor is mesenchymal, and, being so, has propensities for forming tissues of mesenchymal origin. The case of the malignant lymphomas is strictly analogous.

Again recalling fundamental concepts, it cannot be emphasized too strongly that lymphatic leukemia, acute, subacute, or chronic, is but one manifestation of malignant lymphoma, differing only in the circumstance of whether or not the malignant lymphocytes are in the circulating blood in appreciable numbers. As Willis so aptly puts it, "leukaemia is merely an inconstant concomitant of lymphosarcoma, of interest to the haematologist but of no significance in fundamental classification and nomenclature of lymphoid tumors." We do not call tuberculosis of the adrenal gland by a different name simply because it involves the adrenal gland, nor do we recognize metastatic bronchogenic carcinoma as an entity separate and distinct from the primary neoplasm simply because the brain or adrenals fortuitously are the seat of metastatic deposits. Circulating blood is a tissue also and leukemia a

metastasis from a malignant lymphoma. The leukemic manifestations may be the dominant finding, may occur concomitantly with visceral masses, may be present and then disappear, may appear only in the terminal phases of the disease, or may never be present.

With these precepts in mind, we may now turn briefly to an outline of a classification of lymphomas which has been used in the Department of Pathology at the State University of Iowa for several decades. This classification embodies the foregoing basic principles which are neither unique nor original with us. Thoroughly lucid, sound and rational expositions on the subject of lymphomas have been provided in the noteworthy contributions of Willis[6] in England, and Warthin,[5] Herbut and coworkers,[3] and Gall and Mallory[2] in this country. At the expense of being redundant, it cannot be argued too strongly that the various subdivisions of malignant lymphoma contain histogenetically identical growths, differing only in growth rate and degrees of differentiation. Again, to paraphrase Willis: to ascribe to the subdivisions of the lymphoma group different names merely because of their differing degrees of cellular anaplasia or maturity is as if one were to attempt to subdivide skin carcinomas into "epidermocytomas," "epidermoblastomas" and "primitive epithelioblastomas" according to their degree of differentiation. To further emphasize this concept, it would be entirely feasible, in spite of certain basic defects, to grade the lymphomas as Broders[1] has done for certain carcinomas, and as Kernohan and associates[4] have done for astrocytic tumors of the central nervous system. Provided the concept of the basic unity or singleness of the whole group of lymphoid tumors is crystallized and inherent in our thinking, subgrouping of the lymphomas will continue to have descriptive and clinical value. A useful working classification, beginning with the most highly differentiated and progressing to the most primitive and anaplastic form of lymphoma, is as follows:

Malignant Lymphoma.

I. Giant follicular lymphoma (grade 1)
II. Lymphocytic lymphoma (grade 2)
  (a) leukemia—approximately 48 per cent
III. Lymphoblastic lymphoma (grade 3)
  (a) leukemia—approximately 38 per cent
IV. Hodgkin's disease
  (a) lymphoma (grade 1)
  (b) granuloma (grade 2)
  (c) sarcoma (grade 3–4)
V. Reticulum cell sarcoma (grade 4)
  (a) syncytial
  (b) reticular
  (c) stem-cell and monocytic leukemia

The arbitrary grading, as given, principally serves to emphasize the unitarian concept, and while useful to designate approximate degrees of differentiation, is fraught with the same difficulties as is the too rigid grading of other neoplastic diseases. Also, we prefer to designate the entire group of tumors of lymphoid tissue as "malignant lymphoma" rather than "lymphosarcoma" only because of the variation in meaning of the latter term as it is used by different authors.

Although it is not intended that a detailed discussion of the various forms of malignant lymphoma be presented, a few brief characterizations will provide a recapitulation of some of the basic principles which have been discussed thus far.

The giant follicular lymphoma is the best differentiated and most slowly progressive of the entire group. The follicular pattern observed is not a remnant of the previous normal nodal architecture, but is an abortive attempt to form follicles by highly differentiated neoplastic lymphocytes. It is not uncommon for this variant to transform into a much less well differentiated type with a concomitant change in clinical course.

Next in degree of differentiation is the lymphocytic lymphoma which presents a

monotonously uniform histologic picture of rather mature neoplastic lymphocytes but without follicle formation. Leukemia occurs in approximately 48 per cent of these cases, and when present, is usually of the chronic type.

The lymphoblastic lymphoma is still less well differentiated, and, clinically exhibits a more progressive and rapid course than the first two variants. Again, the histologic picture is monotonously uniform, but the majority of cells comprising the tumor are lymphoblasts. Leukemia occurs in approximately 38 per cent of the cases, and when present, is usually of the acute variety.

Several histologic features serve to characterize Hodgkin's disease despite the variable and pleomorphic patterns that are encountered. The lymphoma type blends imperceptibly into the lymphocytic variant of the malignant lymphoma group, whereas at the other end of the differentiation scale, the sarcoma variant of Hodgkin's disease is closely related to certain types of reticulum cell sarcoma. Generally, too, the clinical manifestations parallel the histologic appearance.

The most immature and anaplastic of the entire group of lymphomas is the reticulum cell sarcoma of which there are two principal types. The cells of the syncytial variety arise from the littoral cells of the sinusoids of the reticuloendothelial organs and do not form reticulum. The cells of the reticular variety arise from the reticular cells of the pulp of the reticuloendothelial organs and do form reticulum. Stem-cell or monocytic leukemia may be associated with either variant of reticulum cell sarcoma. For reticuloendothelial cells, they may be well differentiated even though they represent the most immature form or precursor of the lymphocytic series and are usually highly malignant.

In all of these subdivisions of malignant lymphoma, mixed cell types are seen—reticuloendothelial cells in giant follicular lymphoma to lymphocytes in reticulum cell sarcoma. But the stage in maturation at which arrest has occurred, the percentage of intermitotics which has undergone arrest, and the rate of proliferation at the arrested stage will determine the histologic appearance, degree of differentiation, and in large part, the clinical course.

CONCLUSION

It would appear that much of the confusion relevant to tumors of lymphoid tissue is, as is the case in many disease states, largely the result of man-made superstructures of complicated classifications and nomenclature. The lack of dissemination and/or application of basic biologic principles has contributed heavily to the many misconceptions that have pervaded the subject of the malignant lymphomas. The unitarian concept just presented, although confronted by the charge of oversimplification by some, seems justified by the facts as we now know them.

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TREATMENT OF MALIGNANT LYMPHOMA AND BLOOD DYSCRASIAS BY CONVENTIONAL ROENTGEN THERAPY*

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THE use of roentgen therapy in the treatment of malignant lymphoma and blood dyscrasias is founded on years of experience on the part of many therapists. A majority of therapists still feels that this should be the basic modality of treatment in these diseases. The extensive research program being carried on at present with the resultant development of new techniques and new therapeutic tools is prompted by the incompleteness of results obtained in the past. Such intellectual dissatisfaction and unrest is the foundation upon which modern medicine is built. It is not wise, however, to lose sight of the present while gazing into the future. Even if we grant that atomic energy may be the basic power source in the future, civilization would be in a chaotic state should all "old fashioned" methods be immediately discarded, or should we fail to train the present generation in their use. Thus, while the author is in enthusiastic agreement with those workers seeking to improve results of treatment with new methods and new techniques, he also feels it incumbent upon us as teachers and therapists to continue to teach, use, and try to improve the results obtained with roentgen therapy. When new agents of therapy or new techniques have proved their worth and have become widely available, then and then only may we justifiably abandon our present conventional methods of roentgen therapy for these diseases. It is with such a philosophy in mind that this paper is presented.

The therapy outlined here represents only a basic plan, subject to many individual variations and to complete replacement by other methods when this method fails or gives an unsatisfactory reponse.

HODGKIN'S DISEASE

While the pathologic classification of Hodgkin's disease with its various gradations and mingling of types is confusing, the clinical picture is all too familiar. Treatment of this condition with roentgen rays may be classified under four headings:

1. Treatment of lesions localized to a lymph node or a juxtaposed group of lymph nodes with moderately heavy therapy, in an attempt for a long term survival.
2. Treatment of local lesions, and all other commonly involved areas, with mild to moderate roentgen ray dosage.
3. Treatment of widespread disease with doses of the smallest magnitude compatible with relief of symptoms.
4. Treatment of the patient with systemic manifestations with or without significant visceral involvement.

When only a localized lymph node or group of lymph nodes is involved, it has been accepted treatment to give doses varying from a low of 2,000 r in two weeks (Nice and Stenstrom[4]) to 4,000 r over a period of four weeks (Buschke[1]). We have given 200 r or 300 r (in air) per day to one or two appropriate fields, using 120 kv. or 200 kv., depending on the depth of the lesion, and giving a tumor dose of 3,000–3,500 r in ten to fourteen days. Many of our long term survivals fall in this group. Even when such a patient returns with extension of the disease elsewhere, it is unusual for the treated site to show recurrent involvement.

While this has been and still remains our

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philosophy of treatment under these conditions, there are frequent experiences which cast doubt upon the necessity or correctness of such therapy. One such example is that of a woman with involvement of the right supraclavicular lymph nodes only. She received a tumor dose of 3,500 r over a period of two weeks and after twelve years of freedom from disease, developed a mediastinal mass proved by biopsy to be identical with the original lesion. Although she again received substantial amounts of roentgen therapy, her course was rapidly downhill to death within a year.

Another patient, aged thirteen had a proved lymphoma of the cecum. Biopsy was taken, but the mass was not removed. She received only 900 r in air over a period of four days, giving a tumor dose of about 400 r. Now, eighteen years later, she has had no recurrence of her disease. Other similar cases have led us to wonder whether these long term survivals are the results of intensive therapy or simply the unusual manifestation of a notoriously unpredictable disease.

We have had no experience with treatment of all lymph node bearing areas or segmental radiation as advocated by Peters,[5] Hynes and Frelick,[2] and others. Certainly, the five-year survival rates reported by these authors, Peters,[5] 51 per cent, Hynes and Frelick,[2] 36 per cent, are much better than those of Nice and Stenstrom,[4] 25 per cent, Slaughter and Craver,[6] 17.7 per cent, Medinger and Craver,[3] 24 per cent, and our own—25 per cent. It is difficult to understand the rationale of therapy which gives 2,000–3,000 r to involved lymph nodes and only 900–1,200 r to "uninvolved lymph nodes," for without biopsy of each lymph node it is impossible to determine which ones are involved.

Twenty-eight per cent of the patients who come to us with Hodgkin's disease show widespread involvement of cervical, axillary, and inguinal lymph nodes with frequent mediastinal and abdominal lymph node involvement as well. These patients may have no symptoms, other than those caused by pressure of the enlarged lymph nodes. Such patients will receive relief of symptoms from surprisingly small doses, and if such doses are used, the patient may be treated repeatedly, if necessary. Superficial cervical, axillary, and inguinal lymph nodes are usually treated with 3 or 4×200 r in air at daily intervals, using 120 kv., half value layer 2.5 mm. Al. Higher doses seem to add little either to the patient's comfort, or to the length of time before return of symptoms. Many involved lymph nodes will shrink to a small but still palpable mass and remain quiescent for variable periods of time. As long as this condition exists, these patients are not re-treated. Our experience suggests that nothing is gained by continuing the treatment to the point of complete disappearance of the involved lymph nodes.

Another group of patients present themselves with fever, anorexia, weight loss, pruritus, anemia, etc. These patients may or may not have significant lymph node involvement. Particularly in those patients without significant nodal enlargement, radiation usually does not produce a satisfactory remission and these patients are most likely to be aided with chemotherapy. Before the advent of this method, however, total body irradiation with 5 to 15 r in air using 200 kv., 0.5 mm Cu filter and 100 cm. distance was employed. Treatments were given every forty-eight or seventy-two hours, the dose and interval being determined by the symptomatology and blood picture of the patient. Fair results were occasionally noted after such therapy, and this method should be considered for the occasional case that does not respond to more conventional treatment.

MALIGNANT LYMPHOMA

The prognosis in malignant lymphoma, like that in Hodgkin's disease, seems to depend more upon the extent and location of the disease than it does upon the pathologic picture. In fact, the chameleon nature of this group of diseases is such that

statistical analyses based on pathology alone are subject to reasonable skepticism concerning their accuracy. Recently a patient had over a period of three months, pathologically proved giant folicular lymphoma, Hodgkin's type lymphoma, and chronic lymphatic leukemia. Such cases multiply in number directly with the frequency of biopsy. Survival rates taken from the literature all too often reflect only the original diagnosis or the predominant pathology at time of postmortem examination.

In such a relatively stable pathologic process as malignant lymphoma of the reticulum cell type, a wide divergence of roentgenologic response is encountered. Those of the skin, especially of the face and scalp, often show a startling response to single doses of as little as 400 r in air. These lesions usually recur near the edge of the previously treated field. Increasing the dose up to 2,000–3,000 r in air and the field size to the limit of practicality has little effect upon the length or completeness of remission. The same pathologic lesion when it occurs in the orbit, tongue, or antrum may show a long term (five to ten year) remission when treated with tumor doses of 2,500–3,000 r given over a period of ten to fourteen days, but when retroperitoneal lymph nodes are the primary site of the disease, it reacts as a radio-resistant tumor. In one such patient with a palpable abdominal mass, a tumor dose of 4,500 r, delivered in four weeks, resulted in a questionable 10 per cent shrinkage of the mass, and three months later, the tumor was twice its original size, this being confirmed by postmortem examination.

Malignant lymphoma, lymphoblastic or lymphocytic in type, clinically most closely simulates the chronic leukemias. In our experience, heavy therapy, except to lesions about the head, has been abandoned. Intra-oral lesions of the tongue, tonsil, pharynx, nasopharynx and oropharynx may reasonably be expected to show a fair percentage of long term survivals. This result has been accomplished by using tumor doses of 2,000–4,000 r over a period of two to four weeks. Similar lesions elsewhere are usually multiple, but when they are solitary, they are treated in a like manner. The chance of a long term survival is not good in these cases.

In generalized disease of this type involving multiple peripheral and visceral lymph nodes, therapy has consisted of the lowest dosage compatible with satisfactory clinical improvement. For axillary, cervical and inguinal lymph nodes, 3×200 r (in air), using 120 kv., with 1 mm Al filter will result in the complete regression of most lymph nodes. A tumor dose of 600–1,200 r to mediastinal or retroperitoneal lymph nodes has proved satisfactory. One such patient had involvement of the cervical, axillary and inguinal lymph nodes as well as a mediastinal mass. Multiple biopsies from axilla and groin were reported as malignant lymphoma, lymphocytic type. He received a mid-mediastinal dose of 800 r and 600 r in air to cervical, axillary and inguinal areas. With no additional therapy he has now survived eight years without clinical or symptomatic evidence of recurrence.

BLOOD DYSCRASIAS

Our philosophy of the treatment of blood dyscrasias has been tempered by the existing economic situation. Many of our indigent patients come from as far as 300 miles away at state expense. Each visit must be considered from the point of view of the number of patients allowed for hospitalization each year. We cannot, therefore, have these patients either stay in the hospital for long periods of time or return at two to four week-intervals, if they are apparently physically well and economically productive. Because of this factor, we have not been able to treat these patients on the basis of blood cell count alone. Many patients will have a white blood cell count above 50,000 for six months or a year while feeling perfectly well and working full time. In fact, we have seen patients who feel

better with such an elevated count than they do when it is reduced to or near normal.

LYMPHATIC LEUKEMIA

Many patients with lymphatic leukemia present themselves only because of unsightly or functionally disabling enlarged lymph nodes. They have no systemic manifestations of their disease. Such patients are treated with radiation directed into the involved lymph nodes. Three or four times 200 r in air given with 120 kv., 1 mm. Al filtration at daily intervals will cause a satisfactory regression of the lymph nodes and frequently constitutes our only therapy. If the white blood cell count is quite high, 100,000 or more, and especially if symptoms of malaise, weakness, anemia, weight loss, etc., are present, total body or spray irradiation is also used. This is given with 200 kv., 0.5 mm. Cu filter at 100 cm. distance to half the body, either anterior or posterior half at each treatment. Such therapy is given twice per week or on rare occasions in patients with resistant disease it may be given three times a week. Daily white blood cell counts must be taken for the relative variation either up or down is much more important than the actual count. If the white blood cell counts have been 90,000 80,000, 70,000, 60,000 on successive days that patient will not be re-treated until a stable level of the count has been reached. But should they read 90,000 30,000 40,000, 50,000, then that patient will be re-treated. As a rough rule of thumb, subject to so many exceptions as to make it almost but not quite worthless, we try to reduce the original white blood cell count by about 75 per cent. Treatments are started cautiously, usually with 5 r in air to half body. Later therapy is based upon response and the dose may be as much as 50 r in air. Once a dose giving a satisfactory response is established, it is seldom necessary to lower this and it may safely be used as an initial treatment in any future course of therapy.

MYELOGENOUS LEUKEMIA

In myelogenous leukemia the lymph nodes are usually small and physiologically insignificant. The most common physical finding is a huge spleen and frequently symptoms center around this enlarged organ. Using 200 kv., 0.5 mm. Cu filter and an appropriate sized field, such a spleen is treated daily with 100–200 r in air to a total of 900–1,200 r, or until satisfactory regression is obtained. Blood cell counts are taken daily and usually show a satisfactory regression as the spleen shrinks. Occasionally, a dramatic and even frightening drop in the white blood cell count will require interruption of therapy regardless of the condition of the spleen.

Many various situations are encountered that modify this therapy and no hard and fast rules can be outlined. While this essay deals with roentgen therapy, it must not be construed to mean that we consider this to be the only therapy or even the preferable therapy in any given case.

CONCLUSION

1. This entire group is comprised of cases that are highly unpredictable as far as prognosis is concerned.

2. Localized lymphoma should be treated with moderately heavy roentgen therapy (3,000–3,500 r tumor dose in two weeks). There are enough long term survivals with small dosage to cast some doubt on the validity of this type of therapy, but not enough, however, to warrant its discontinuance.

3. In the case of the lymphomas, site and extent of disease are more important in prognosis than is the pathologic picture.

4. Because of the interchangeable nature of the pathology of these diseases, statistics based on cell type must be regarded with some skepticism as to their validity.

5. Many blood dyscrasias may be controlled for a variable time with roentgen therapy alone.

6. In blood dyscrasias the patient's symptoms form a satisfactory criterion for

treatment, regardless of the blood cell count.

7. The therapist must be familiar with *all* methods employed to treat this group of diseases and be prepared to use or recommend their use whenever type of disease or lack of response suggest they might be advantageous.

8. Until a time when new methods and agents prove their unquestioned superiority and until they are widely available, it is advisable to use and attempt to improve present methods employing roentgen therapy.

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DISCUSSION

DR. GEORGE COOPER, JR., Charlottesville, Virginia. Perhaps in no field of radiation therapy do the results depend more heavily upon the physician's skill and judgment than in the one under discussion, although palliation only is attainable. Peculiarly radiosensitive lesions are being dealt with. There is little or no question of having to introduce so many thousand r in so many days in order to achieve a cancerocidal effect. Instead we have to try to administer to each individual, in each episode of his disease, the course of therapy which will relieve his symptoms and produce as long a remission as possible with a minimum of disagreeable side effects.

This means unusually close supervision by the radiologist, with day-by-day planning of therapy.

As Dr. Elkins has so aptly phrased it, recommendations for therapy in this group of diseases represent only a basic plan. Therefore, to every statement he has made or that anyone else can make, exceptions can be cited and arguments raised, and I am sure that if time permitted, most of the people in this room would have comments about which they would like to express themselves.

However, about the localized lymphomas, the doubt that Dr. Elkins expresses concerning the validity of moderately heavy dosage, though reasonable, certainly should not tempt one to resort to diminishing the moderately heavy dosage program.

Dr. Elkins has commented that it does not tempt him to reduce his dosage, and I certainly feel no temptation to reduce mine, because the doses now in general use produce very little ill effect, none of real consequence, and it is in this group of patients so treated that we have recorded many of our long-term survivals.

In general, a good many radiologists would employ smaller daily dosages, at least initially, in the treatment of these diseases than Dr. Elkins has mentioned. Certainly excessively rapid resolution of these remarkably sensitive tumors, particularly when they are numerous or bulky, is often accompanied by a systemic reaction. This is probably due more to absorption of breakdown products of the tumor than the radiation *per se*, but reaction can be minimized by withholding radiation for a day or so or by sharply reducing the daily dose at least temporarily.

REVIEW OF SEVENTEEN YEARS' EXPERIENCE WITH TRANSVAGINAL ROENTGEN THERAPY IN CERVICAL CANCER*

By RALPH M. CAULK, M.D.†
WASHINGTON, D.C.

DURING the years 1937 through 1953 inclusive, a total of 733 patients applied for and received treatment for cervical cancer in the Department of Radiotherapy at the Garfield Memorial Hospital, Washington, D.C. In all of these patients, histologic proof of the diagnosis was established. All of the cases represent clinical cancer, *i.e.*, they had signs, and/or symptoms consistent with the diagnosis.

The patients are from both private and clinic sources, representing all social and economic levels. Thirty-eight per cent of the patients were of the Negro race, which is the approximate prevalence of that race in Washington, D. C. today. In other words, the material represents the disease as it probably exists in the Community *i.e.*, the metropolitan area of Washington, D.C.

There was no selection of cases over which the department had any control. The policy of the department prior to 1948 was to accept all cases regardless of the extent of the disease, racial, social or economic status. Since 1948, a few cases have been rejected for economic reasons.

The material has been divided into clinical stages, based upon the revised League of Nations classification of 1937. The percentage incidence by stages was as follows: Stage I, 28 per cent; Stage II, 41 per cent; Stage III, 29 per cent; Stage IV, 4 per cent; and modified, 7 per cent.

A modified group has been added to segregate the cases that fall into the following categories: 1. Those cases in which a portion of the treatment was given elsewhere and was unorthodox by our standards; 2. uncontrolled disease, discovered either incidentally at surgery or persisting after definitive surgery; 3. uncontrolled disease treated by radiation therapy elsewhere.

The following principle suggested in the League of Nations Hand Book has been utilized in the staging: "In determining whether an individual case should be considered as an advanced example of a certain stage or an early example of the more advanced stage, it should be made a general rule to allocate cases to the prognostically more favorable stages, in order not to raise unduly the rates of earlier stages." The practical application of this principle undoubtedly results in the allocation of considerably more cases to Stage I and Stage II than is ordinarily reported in the literature.

The results of treatment in the entire group of cases are shown in Table I. In this table, and in the following tables, all

TABLE I

ROENTGEN THERAPY—CERVICAL CANCER
1937 through 1953

Total			733 Cases
Minimum 5 Year Observation			614 Cases
Indeterminate Group			43 Cases
A. Treatment not definitive			22
B. Untraced under 5 years (3%)			21
Determinate Group			571 Cases
Stage	Cases	Survivals	%
I	139	94	67
II	248	89	36
III	130	22	17
IV	17	0	0
Modified	37	3	7
5 Yr. Survival Rate Determinate Group		571/208	36%
5 Yr. Crude or Absolute Survival Rate		614/208	33%

* Presented at the Fifth-fifth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 21–24, 1954.
† From the Radiological Clinics of Drs. Groover, Christie and Merritt, Washington, D. C.

patients in whom the treatment was not definitive have been placed in the *indeterminate* group. The term *treatment not definitive* refers to those patients who died either of their disease or other causes before sufficient treatment was given to be of any benefit. It also includes those patients who voluntarily discontinued treatment for various reasons. These patients have all been traced and all are dead. It is noted that only 3 per cent of the total have been lost to follow-up. This high percentage of follow-up renders the statistics quite valid.

The period 1937 to 1953 inclusive was selected for study because it was at the beginning of this time that the late Dr. E. A. Merritt,[4,5] with whom I was then associated, instituted aggressive treatment towards cervical cancer by means of transvaginal roentgen therapy. Of the entire 733 cases treated during this period, this modality was used in 82 per cent. The utilization of transvaginal roentgen therapy in this group, by stages was as follows: Stage I, 96 per cent; Stage II, 92 per cent; Stage III, 72 per cent; Stage IV, 40 per cent; and modified, 52 per cent.

It is obvious that a considerable degree of selection ensued, utilizing the various combinations of treatment methods available to us. These combinations fall into the following categories:

1. External and transvaginal roentgen therapy only.
2. External and transvaginal roentgen therapy combined with intracavitary radium.
3. Transvaginal roentgen therapy only, combined with intracavitary radium.
4. Transvaginal roentgen therapy only.
5. Cases receiving no transvaginal roentgen therapy.

The technique utilized in this material has been previously described by this author.[1,2] It is not felt necessary for the purpose of this paper to discuss this aspect.

EXTERNAL AND TRANSVAGINAL ROENTGEN THERAPY ONLY

By far the largest category received external combined with transvaginal roentgen therapy only. The results of treatment in this group are shown in Table II.

TABLE II

ROENTGEN THERAPY—CERVICAL CANCER

External Combined with Transvaginal
1937 through 1953

Total			365 Cases
Minimum 5 Year Observation			318 Cases
Indeterminate Group			14 Cases
A. Treatment not definitive			2
B. Untraced under 5 years			12
Determinate Group			304 Cases
Stage	Cases	Survivals	%
I	55	39	71
II	161	65	40
III	71	17	24
IV	5	0	0
Modified	12	2	16
5 Yr. Survival Rate Determinate Group		123/304	40%
5 Yr. Crude or Absolute Survival Rate		123/318	39%

It is only fair to state that 25 cases of this entire group received a small dose of local radium to the cervix. This procedure was done in some of the earlier cases and consisted of the packing of two parallel tubes of radium against the cervix. Each tube contained 50 mg. of radium with an effective length of 4 cm. This rather simple applicator was packed against the cervix for twelve hours. The filtration was 1 mm. of gold. This procedure was done in those cases where the bleeding was quite severe and was used before we soon learned that the bleeding could be controlled much easier with the transvaginal technique only, associated with packing the vagina for a matter of four or five days. This procedure is in many instances done on an outpatient basis. It is not felt that this small dose of radium in any way contributed to the long-time survivals in this group.

EXTERNAL AND TRANSVAGINAL ROENTGEN THERAPY COMBINED WITH INTRACAVITARY RADIUM

The results of treatment in this group are shown in Table III. It would seem that the addition of intracavitary radium to this

TABLE III

ROENTGEN THERAPY—CERVICAL CANCER

External Combined with Transvaginal and Intracavitary Radium
1937 through 1953

Total			108 Cases
Minimum 5 Year Observation			76 Cases
Indeterminate Group			2 Cases
A. Treatment not definitive			0
B. Untraced under 5 years			2
Determinate Group			74 Cases
Stage	Cases	Survivals	%
I	15	11	73
II	44	17	38
III	12	3	25
IV	0	0	0
Modified	3	0	0
5 Yr. Survival Rate Determinate Group		31/74	41%
5 Yr. Crude or Absolute Survival Rate		31/76	40%

group has contributed relatively little to the survival rate. The figures, of course, are rather small and certainly not of true statistical significance.

In the past six years, the use of supplementary intracavitary radium has been utilized more frequently. Thirty-six per cent of Stage I and 43 per cent of Stage II lesions receiving transvaginal therapy have also received intracavitary radium. In 15 per cent of the Stage III lesions, intracavitary radium has supplemented the transvaginal roentgen therapy, while in the Stage IV and modified groups, the figures are too small to be of any significance whatsoever. This author[3] has reported elsewhere the results of transvaginal roentgen therapy in cancer of the cervical stump, in which of course, intracavitary radium cannot be used for physical reasons.

The amount of intracavitary radium used as a supplement has varied considerably over the years. The present plan, which seems to be quite practical and devoid of added complications, is to add sufficient intracavitary radium to administer 2,000 gamma r at a point 2 cm. lateral to the internal os. That portion of the tandem adjacent to the external os is left blank for a distance of 15 mm. in order not to overirradiate an area that has had adequate radiation from the transvaginal roentgen therapy. It is believed that intracavitary radium is certainly necessary as a supplement to the total treatment in those cases of endocervical cancer and in those cases in which the disease has already spread to the interior of the uterus. Supplementary radium is also indicated when the vagina is less than average size, and as a consequence can only physically accommodate a small transvaginal speculum, which in turn limits the dosage in the pericervical area.

TRANSVAGINAL ROENTGEN THERAPY COMBINED WITH INTRACAVITARY RADIUM

Table IV shows the results of treatment in this small group of cases. This is a select group of primarily obese patients in which it was felt that only minimal benefit could be obtained by the addition of external roentgen therapy. Even the Stage I survivals are lower with this approach than the average, because in using this criterion for selection a considerable number of rather advanced Stage I lesions were treated in this fashion. One would not anticipate long-time survivals in Stage II lesions treated with localized techniques of this type.

TABLE IV

ROENTGEN THERAPY—CERVICAL CANCER

Transvaginal Combined with Intracavitary Radium
1937 through 1953

Total			33 Cases
Minimum 5 Year Observation			20 Cases
Indeterminate Group			0 Cases
A. Treatment not definitive			0
B. Untraced under 5 years			0
Determinate Group			20 Cases
Stage	Cases	Survivals	%
I	12	7	58
II	6	1	16
III	1	0	0
IV	0	0	0
Modified	1	0	0

TRANSVAGINAL ROENTGEN THERAPY ONLY

Table v shows the treatment results in a very interesting group that received no radiation other than by the transvaginal approach. This is by and large a rather highly selected group because of the fact that they were, for the most part, early and relatively early lesions. On the other hand, there are several survivals in this group of full-blown, extensive Stage I lesions treated with this single technique only by virtue of the fact that they were obese subjects. It is of particular interest to note that in the Stage I lesions in this group, selected for transvaginal treatment only, the salvage rate was approximately that obtained in cases treated by our most aggressive techniques. I believe the transvaginal technique alone is sufficient to produce a high survival rate in early Stage I lesions in which the vagina will physically accommodate a medium or large sized speculum. It is a most gratifying experience to indulge in a long term follow-up of patients who have been treated for a serious, cervical cancer with eight treatments given on an out-patient basis. Again, it is only fair to state that in this group there were two Stage I lesions that received a small dose of supplementary vaginal radium by the technique and for the indications described above.

It is at the same time disheartening and enlightening to know that five of the Stage I lesions in this group died in the fourth year of other causes and were clinically free of their cancer.

TABLE V

ROENTGEN THERAPY—CERVICAL CANCER

Transvaginal Only
1937 through 1953

Total			97 Cases
Minimum 5 Year Observation			85 Cases
Indeterminate Group			5 Cases
A. Treatment not definitive			3
B. Untraced under 5 years			2
Determinate Group			80 Cases
Stage	Cases	Survivals	%
I	50	34	68
II	16	2	12
III	11	0	0
IV	0	0	0
Modified	3	1	33

TABLE VI

ROENTGEN THERAPY—CERVICAL CANCER

No Transvaginal
1937 through 1953

Total			130 Cases
Minimum 5 Year Observation			115 Cases
Indeterminate Group			22 Cases
A. Treatment not definitive			17
B. Untraced under 5 years			5
Determinate Group			93 Cases
Stage	Cases	Survivals	%
I	7	3	43
II	21	4	19
III	35	2	5
IV	12	0	0
Modified	18	0	0

CASES RECEIVING NO TRANSVAGINAL ROENTGEN THERAPY

Table VI shows the results of treatment in those cases that received no transvaginal roentgen therapy. The very poor survival rate in this group by stages indicates the degree of selection that has been employed in all the material. It is obvious that transvaginal roentgen therapy is not physically or practically possible in a certain number of cases, particularly those that are far advanced and have disease involving the vaginal walls and those in which the vagina is too small to accommodate a speculum of necessary size.

COMPLICATIONS

For the purpose of evaluating complications, the current survivors of those patients treated with the more modern techniques of 1948–1951 inclusive were evaluated. Only the complications occurring in the area traversed by the transvaginal beam have been considered. This minimal two year observation eliminates most of the cases in which the complication might be considered as compatible with uncontrolled disease.

Forty-four cases are available for study with this criterion for selection and of these:

1. Twenty-one required tincture of opium to control diarrhea during the course of treatment.
2. Four developed rectal ulceration and stricture requiring surgical resection.
3. Three developed symptomatic narrowing of the rectum that has not required surgical intervention.
4. Seventeen have vaginal atresia of a mild degree in the apex of the vault; eight have atresia of moderate extent; and thirteen have a marital vagina.
5. Two developed necrosis of the vaginal wall, one of which required surgery.
6. No cases have had symptoms at any time referable to radiation effects in the bladder, and none of vesicovaginal fistula.

The most serious complications in this group have been ulceration and stenosis of the rectum requiring surgical intervention. To date they have been satisfactorily controlled by the operative procedure.

The record would indicate that none of the cases that were treated by the transvaginal technique alone developed these complications, and, as a matter of fact, none of them even had sufficient diarrhea to require opiates for control. It becomes apparent, therefore, that these complications are caused by the supplementary external roentgen therapy. In order to increase the dosage supplemented by the external roentgen therapy to the area immediately adjacent to the cervix, the external fields were very closely approximated in this material and this factor alone is now believed to be responsible for this rather high incidence of rectal reaction.

By placing a heavy strip of lead, 4 cm. in width, in the mid-line both anteriorly and posteriorly so that this area could not possibly be irradiated, we have reduced the symptoms of diarrhea to an absolute minimum, and as a consequence, one would not anticipate the development of any late rectal stricture such as we have reported. With this procedure, of course, one must recognize that this compromise may result in a diminished survival rate. On the other hand, one might very well adopt the philosophy that the 10 per cent incidence of a surgically correctable complication is a calculated risk that can rightfully be assumed in the aggressive management of cervical cancer. The total absence of bladder complications, either early or late, is most gratifying and maintains the total incidence of serious complications at a relatively low level.

DISCUSSION

It would seem that the transvaginal technique from a statistical standpoint is a potent cancerocidal approach in the vast majority of cases. The results in the group treated with this method only indicate that under ideal conditions, *i.e.*, early Stage 1 lesions, it is probably the simplest and most economical method of treating cervical cancer. Under less ideal conditions and with a wide range of applicability, the technique may be regarded as an effective substitute for the various types of vaginal radium applicators.

The technique possesses certain advantages, *viz.*,

1. It is economical in that the treatment is done on an out-patient basis, thus eliminating the cost incidental to hospitalization.
2. It is simple and easily mastered.
3. The roentgen apparatus necessary is widely available and the specific apparatus, *i.e.*, the specula, cones, etc., require only a small capital investment.
4. The complications, as a whole, are probably less than in other aggressive techniques.
5. The full responsibility for the treatment is placed in the hands of the radiologist where it rightfully belongs.

CONCLUSION

The total experience with a large series of cases of cervical cancer has been related. It is felt that the cases represent the disease

as it prevails in a large metropolitan area, and selection, if such exists, is of the "community type." Eight-two per cent of this entire group of cases received roentgen therapy by the transvaginal approach.

The statistical results, complications, advantages of and indication for this technique have been described.

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DISCUSSION OF PAPER BY DR. CAULK

Dr. Charles L. Martin, Dallas, Texas. When Dr. Caulk requested that I discuss his paper, I asked to be excused because I do not use transvaginal roentgen therapy, believing that a flexible radium technique carefully selected to fit each case constitutes a better method. However, I accepted the assignment and it seems that I must defend my position.

The completeness of Dr. Caulk's statistical survey of such a large number of patients and his excellent cure rate deserve the highest praise. One must carry out such a project personally to appreciate the monumental amount of hard work involved.

I was one of Dr. Merritt's greatest admirers and he invited me to visit his clinic at Garfield Hospital after he had his combined roentgen technique well under way. At that time I was impressed by the fact that many of his patients seemed quite ill and for that reason I decided against the adoption of his technique. No doubt, Dr. Caulk has reduced the number of serious sequelae but his figures for his more recent group of 44 cases treated from 1948 to 1951 indicate that tincture of opium was required for the proctitis produced in half of them and that 9 or 22.7 per cent of the series developed serious complications in the rectum or vagina. In our own clinic where a combination of electrocoagulation, low intensity radium capsules, and radium needles is used with moderate amounts of external roentgen therapy, serious sequelae have been almost completely eliminated and our over-all five year cure rate averages a little over 40 per cent.

I am inclined to agree with Dr. Caulk that transvaginal roentgen therapy alone is an effective method for the treatment of certain early Stage I lesions, but I must completely disagree with his statement that "under less ideal conditions and with a wide range of applicability, the technique may be regarded as an effective substitute for the various types of vaginal radium applicators." I fear that this statement will be interpreted by many roentgenologists who do no radium therapy to mean that they can now treat all cancers of the cervix efficiently in the office with roentgen therapy alone. Since Dr. Caulk now uses intracavitary radium in 36 per cent of his Stage I cases, 43 per cent of his Stage II cases and 15 per cent of his Stage III cases, he obviously would not agree to such an interpretation. To further emphasize this point, please allow me to again call attention to his contraindications to the combined type of roentgen therapy. They are a small vagina, obesity, vaginal involvement and endocervical or intrauterine cancer.

It is our custom to start the treatment of every patient while she is under an anesthetic on the operating table. At that time presenting bleeding tumor tissue is removed by electrocoagulation, the cervical canal is located if possible and the extension of the neoplasm within the cervix and uterus, as well as extrauterine extensions, are accurately mapped out. A plan of radium therapy is then started designed to irradiate all of the lesions found. With low intensity radium needles and capsules available the radium sources can be placed in the cervix, the uterus, the parametrium, and the vaginal walls, if need be, so that the contraindications listed by Dr. Caulk need not be considered. The roentgenologist who plans to use transvaginal roentgen therapy as one of his most important procedures should remem-

ber that a cervical carcinoma which seems quite localized on ordinary pelvic examination may be found to extend beyond the reach of this technique when a thorough examination is done under anesthesia.

Dr. Caulk (closing). I want to thank Dr. Martin for discussing this paper. Inasmuch as it was primarily of a statistical nature, I felt that Dr. Martin would give a very excellent discussion.

Actually, there are two points of controversy between us. The second one, I shall take up first.

Dr. Martin stated that I consider the transvaginal technique contraindicated in endocervical cancer, cancer that has spread to the endometrium and cancer that has spread to the vaginal wall. He quoted me incorrectly in this respect; as stated in the paper, I feel that the transvaginal technique must be supplemented with intracavitary radium in endocervical and intrauterine spread, and I also stated that local radium application must be used when the disease has spread to the vaginal wall.

Regarding complications, I pointed out to you that one might adopt the philosophy that surgically correctable complications may be a calculated risk that must be rightfully assumed, if cervical cancer is to be treated aggressively. I commend for your reading, a very excellent article by Dr. Martin which appeared in the *Texas State Journal of Medicine*, in the issue of December 1948, entitled "New Developments in the Irradiation Therapy of Cancer of the Uterine Cervix." In this article, Dr. Martin not only reported his results, but he stressed in particular his low incidence of complications.

Dr. Martin uses a very simple classification which by definition is easily comparable to the revised League of Nations classification that I have utilized. In the article, he stated that when all the cases that had neither vaginal wall involvement nor demonstrable involvement of the parametria were included, his five-year survival rate was 61 per cent. This classification is identical with my concept of the revised League of Nations Stage 1, in which we have just now reported 139 cases, with 94 five-year survivals or 67 per cent five-year survival rate. I believe that a 6 per cent increase in survival rate is statistically significant in a group of cases of this number.

Furthermore, Dr. Martin stated that when the disease had spread to the vaginal wall or showed invasion of the parametria or other evidence of extension beyond the cervix, that his survival rate was 16.6 per cent. In the material herein presented, we had 432 cases in that category with 114 or a 26 per cent five-year survival rate. This is an increase of 10 per cent over his figures.

It would seem in the two instances that we are both talking about the same type of material. Such being the case, I firmly believe that the added risk of complications that we have assumed, is justified in view of the statistically significant increase in control of this disease.

SOLITARY MYELOMA OF BONE*

A CASE REPORT

By P. E. RUSSO, M.D., *and* B. H. BROWN, M.D.

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SOLITARY myeloma of bone, also referred to as solitary plasma cell myeloma of bone or plasmocytoma, should not be confused with plasmocytoma of the soft tissues which occurs in the upper respiratory and digestive tracts and is considered a nonosseous tumor. Until 1950 when Christopherson and Miller[1] reviewed the literature on this subject, only 94 cases verified by histologic examination had been reported. A precise correlation between solitary myeloma and multiple myeloma is still lacking.

Because this bone lesion is still a rarity and since its course is unpredictable, a single case report which has been under observation for over seven years may be justified. The location of the lesion in this case did not permit surgical eradication so that it was treated with roentgen radiation, which adds to the interest of this report.

REPORT OF CASE

O.C. 156–839. A twenty-six year old Indian female patient was first admitted to University Hospitals on August 3, 1949, with a history of pain of the left hip which radiated down the lateral aspect of the thigh. The onset of these symptoms had occurred four years previously, in 1945 following a fall while walking downstairs, striking the buttocks. She was taken to another hospital where roentgen examination revealed a compression fracture of the first lumbar vertebra. She was placed in a body cast for one month and wore braces for six months. Since that time the pain in the left hip and leg had become progressively worse.

Examination at this time revealed paresthesia over the anterior aspect of the left thigh. A vague sensory loss was noted in the L1–L2 dermatomes with mild pain on straight leg raising. The deep tendon reflexes were normal. A spinal puncture revealed a complete block with the Queckenstedt maneuver. Spinal fluid examination was reported as showing protein 200 mg. per cent, 4+globulin, negative Wassermann test and repeated urine examinations were negative for Bence Jones proteins. Complete blood cell counts were normal; total proteins 7.55; A/G ratio 6.0/1.55.

Roentgen Examination. There was evidence of a severe deformity of the body of the first lumbar vertebra, resulting in a kyphosis at this level. The vertebral body was flattened and expanded in its horizontal plane. The bone structure looked decalcified and multiple cystic areas were present. The pedicles and laminae of this vertebra showed similar involvement. The vertebrae above and below this level were normal in appearance in every respect. Comparison of these films was made with those taken on September 11, 1945, almost five years previously. It was apparent on the original films that a pathologic compression fracture of the first lumbar vertebra was present. There was involvement of the entire vertebra with multiple cyst-like areas. Since that time further collapse of this vertebra had occurred. Myelography was performed three days after admission which showed a complete block at this level of the second lumbar segment. A benign giant cell tumor or hemangioma of the first lumbar vertebra was suspected (Fig. 1, 2 and 3).

Operative Findings. An exploratory laminectomy was performed on August 16, 1949 in an effort to relieve the block and to obtain tissue for microscopic examination. The spinous process of the first lumbar vertebra was eggshell like in consistency and could be broken easily using only thumb forceps. The laminae were similarly involved. The surgeon felt certain that he was dealing with some type of malignant tissue and requested frozen sections. Examination of this tissue was reported as an undifferentiated malignant neoplasm of bone. Tissue having a bluish and firm consistency was removed from within the spinal canal thus relieving the obstruction. It was thought by the orthopedic and neurologic surgeons that any attempt to perform a spinal fusion at this time was inadvisable. A week later the patient was

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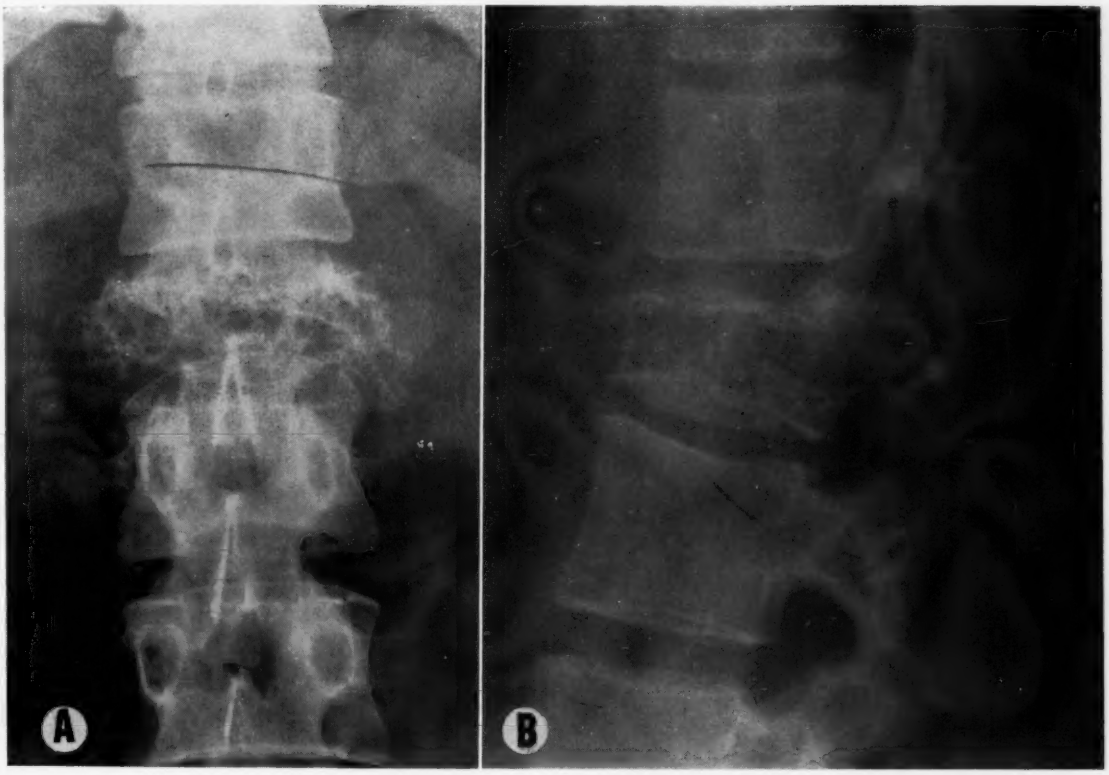

Fig. 1. (*A* and *B*) Compression fracture sustained after the injury July 30, 1945. The first lumbar vertebra is deformed and decalcified. Cystic areas are noted of the body, pedicles and spinous process of this vertebra indicating presence of a pathologic process.

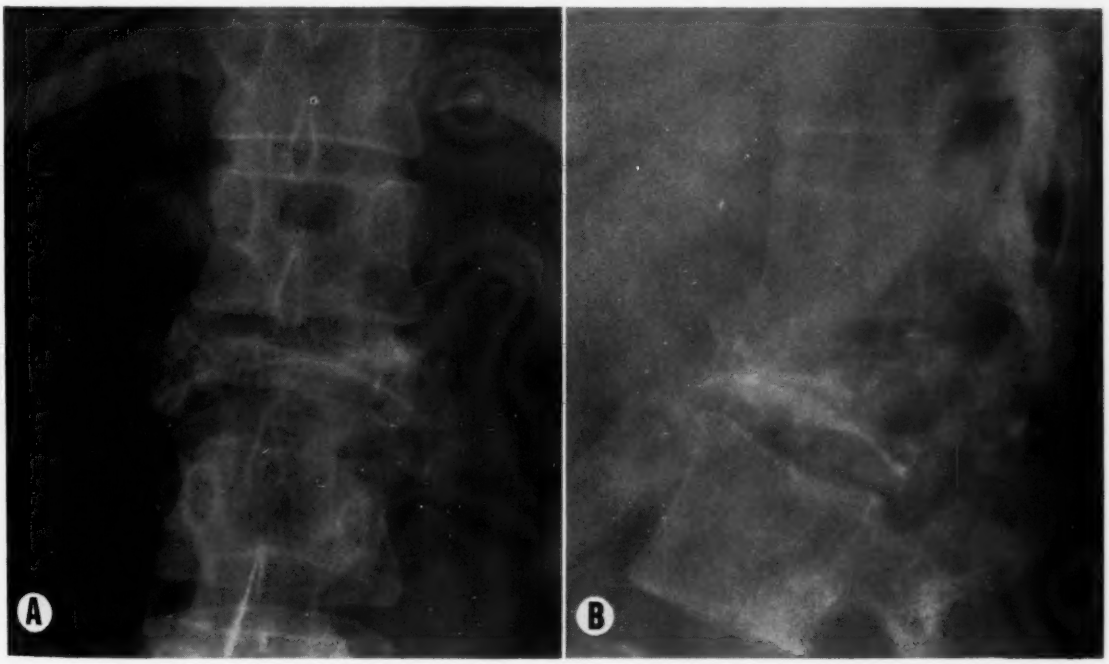

Fig. 2. (*A* and *B*) Films taken August 4, 1949 reveal that the deformity of the body is more severe. The pedicles, laminae and spinous process show a greater degree of involvement.

FIG. 3. Myelogram indicating level of complete block at the level of L2 interspace.

immobilized in a body cast and a window 10 by 10 cm. was cut out over the site of the skin incision and another window in the epigastric area at the same level, with the purpose of administering roentgen therapy to the lesion (Fig. 4).

Pathologic Report. Gross: The specimen consisted of numerous fragments of osseous and soft tissue. The soft tissue was grayish white and red. Four representative parts of the soft tissue and one portion of the bone were preserved for microscopic studies.

Microscopic Aspect. The different parts which were studied were essentially similar, consisting largely of neoplastic cells exhibiting no special structure. There was not much interstitial tissue and the cells were lying very close to each other. Anaplasia and marked pleomorphism were remarkable. The average size of the the cells was approximately 25 microns in diameter. Some cells with a single nucleus which could be occasionally seen measured 125

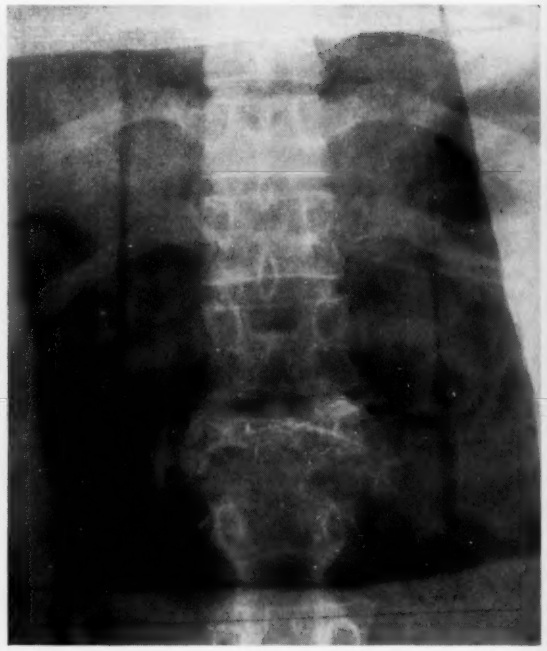

FIG. 4. Shows windows in body cast used to administer deep roentgen therapy.

microns. The aspect of the cells was that of plasma cells. The arrangement of chromatin was characteristic for the plasma cell. The nuclei were eccentrically placed in the oval

FIG. 5. Examination on April 23, 1952 about two and one half years later shows that some recalcification and bone regeneration of the first lumbar vertebra have taken place.

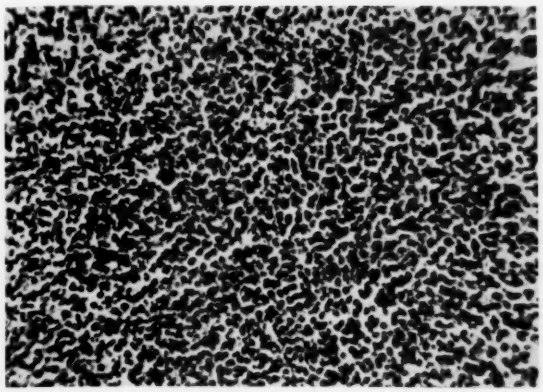

FIG. 6. Low power photomicrograph.

cell. The cytoplasm revealed slight granularity and was basophilic. Some large and small lymphocytes seemed to be a part of the tumor itself and did represent an inflammatory reaction. Occasionally multinucleated giant cells could be detected.

Diagnosis. Plasmocytoma (plasma cell myeloma) (Fig. 6 and 7).

Treatment. Deep roentgen therapy was started on the tenth postoperative day. A daily dose of 300 r was given through the windows in the body cast, using the following factors: 200 kv. 18 ma., 50 cm. distance, filter of 1 mm. Cu plus 1 mm. Al, field 6 by 8 cm. The patient was discharged from the hospital on August 29, 1949, but radiation therapy was continued in an ambulatory way. A dose of 2,400 r, measured in air, was delivered to the anterior and posterior portals, with a tumor dose of approximately 1,800 r.

The patient remained in a body cast for approximately ten months and after that was fitted with a metal back brace. She has remained asymptomatic since the time of her operation. Complete clinical and roentgenographic examinations conducted at six months intervals have failed to show any progression or dissemination of her disease.

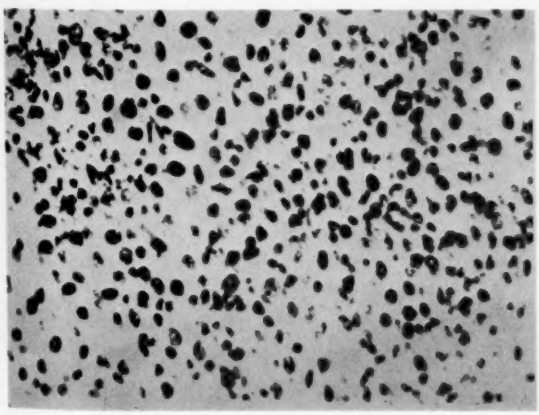

FIG. 7. High power magnification shows characteristics of plasma cells.

DISCUSSION

It is not within the scope of this paper to review the literature on this subject, though some references are listed.[1–7] Rather we wish to re-emphasize certain salient features of solitary bone myeloma which has been established as a disease entity. The clinical observation of pain, tumor mass formation, and spontaneous fracture gives no indication of the true cause of these manifestations. The roentgen findings likewise have no particular characteristics and may simulate those of a giant cell tumor or bone metastasis; it would be most hazardous to rely on them for a diagnosis. Willis has offered the following criteria for a correct diagnosis in these cases: "(a) microscopical identification of the growth, (b) exclusion of the possibility that the tumor is merely the first sign of generalized myelomatosis; (a) involves exploratory operation, and (b) complete and repeated radiographical examination of the whole skeleton." Additional studies such as sternal marrow puncture, urine examination for Bence Jones proteins and serum A/G ratio may be of value. Willis believes that in those cases which show no dissemination within the first year a more favorable prognosis is justified.[7] In contrast to this opinion Lichtenstein states that the disease may become generalized at any time and that after a duration of ten years there are only rare instances of survival.[4] Christopherson and Miller believe that if dissemination occurs it is during the first three years.[1]

Treatment of this lesion has been successful with surgery or irradiation, or a combination of the two. In accessible lesions resection, excision and curettement of the lesion has been advocated. Irradiation also has been used with equally good results in inaccessible locations. In the present

case enough tumor was removed to relieve the pressure on the cord and to re-establish the circulation of the spinal fluid. The remaining tumor was subjected to irradiation. The patient undoubtedly profited by both of these procedures and it would be difficult to evaluate the proportional benefit attributable to each.

It has been of interest for us to note what changes have taken place at the site of the monostotic lesion. In the original film the first lumbar vertebra is decalcified, cystic and deformed. Involvement of the body, pedicles, laminae and spinous process is seen. After a period of four years the body of the vertebra is more flattened and spread out. The cystic changes and the degree of decalcification has become more extensive. Following surgery and roentgen radiation interval films show very little change which can be observed. The body of the vertebra remains markedly deformed. A slow process of recalcification and osteoid regeneration of the diseased vertebra has occurred (Fig. 5).

SUMMARY

A case of solitary myeloma of bone involving a lumbar vertebra is presented. This case has been under observation for approximately seven years and the lesion has remained localized. The diagnosis was established by tissue examination obtained by surgical intervention to relieve a spinal cord block. Deep roentgen therapy to the lesion has kept the patient asymptomatic for the last three years. The exact onset of this disease is difficult to determine although films taken seven years previously, when the patient suffered a pathologic fracture, would indicate that the disease was present at that time.

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We are indebted to the McBride Bone and Joint Hospital, Oklahoma City, for use of the original films in this case. Also, we wish to express our gratitude to Dr. Howard Hopps and to the other members of the Department of Pathology for their help in the preparation of the microphotographic illustrations. We wish to thank Dr. Jess Herrmann of the Neurosurgery Department for the description of the operative findings.

ADDENDUM

Patient was contacted 9-14-56 and is still doing well eleven years after onset of this condition.

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ROENTGEN THERAPY OF PLANTAR WARTS

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THE value of irradiation in the treatment of plantar warts has been recognized by most radiologists for years. The majority of other physicians, however, remains to be convinced of its therapeutic benefits.

Pendergrass and Hodes[5] gave a very complete resume of the treatment of inflammations as a whole. They considered the verrucae to be of virus origin. Andrews[1] states, "The common wart with its plane, the senile or seborrheic wart and the moist or fig wart are all considered to be manifestations of a virus infection."

The verruca plantaris, also called papilloma of the sole, generally forms at points of pressure on the ball of the foot. It may, however, be scattered over the sole, irrespective of pressure. Sometimes plantar warts are grouped, or several contiguous warts fuse so that they appear as one until the keratotic surface is shaved off. They seem to spread from the mother wart. The cores are soft and pulpy and are surrounded by a firm horny ring, occurring in no other form of wart. Over the surface of the core may be seen multiple small black points. These are a result of hypertrophied papillae containing highly distended blood spaces, largely filled by hematogenous hyalin. Plantar warts are frequently mistaken for callus. In any painful callus careful search should be made for a spot that glistens in reflected light. On the weight bearing surfaces the wart does not project above the skin as on the skin elsewhere.

The incidence of plantar warts has appeared to increase in recent years, possibly due to the increasing popularity of sports and the frequent use of public shower baths and locker rooms by a large number of people. This may also account for the increasing frequency in persons of high school and college age.

The symptoms of plantar warts vary from the sensation of a "pebble in the shoe" to marked disability. Treatment has often been delayed because of failure of the physician to recognize the condition or because of the indiscriminate use of such palliative measures as acids, frequent parings and callus file.

The present treatment of plantar wart apparently does not lie within the field of any one medical specialty. It is a fact, however, that the gratifying results which follow the use of roentgen rays have led to general acceptance of this method which is painless in application and usually produces relatively litttle discomfort during the reaction stage. Pendergrass[5] mentions that various caustics have been used with varying success, among which are listed, salicylic acid, glacial acetic acid, trichloracetic acid and chromic acid. Carbon dioxide snow and electrolysis have also yielded fair results. Early reports pertaining to radiation therapy were unusually encouraging. Pendergrass reported 208 patients receiving roentgen therapy with excellent results in 98 per cent of the cases. He used contact therapy and dosages of 2,000 r to 2,500 r. Pohle[7] has recommended doses of 410 r to 680 r, using low voltage roentgen rays. Degrais and Bellot,[2] using gamma rays of radium in 87 cases, reported good results in each case. Marks and Franseen[3] reporting 175 cases, 158 of which were treated by radium, stress the dangers of repeating the treatment if the first attempt is not successful. We believe low voltage roentgen rays with low filtration are more effective. Popp and Olds[8] reported 63 per cent good results using 80 kv., target-skin distance of 40 cm. and a dose of 1,200 r. The low dosage may account for the low percentage of good results.

In our clinic during the past twenty-five

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years, irradiation has been the treatment of choice. The requirements of Osborne and Putnam[4] are carefully observed. These are: first, the paring of the horny or thickened surface with a scalpel or a callus file; secondly, the close approximation of lead foil to the periphery of the wart and thirdly, immobilization of the foot during treatment. Persons over fifty years of age are not treated because of possible changes in skin nutrition. If the wart is under 8 mm. in diameter, a single treatment is given using a dose of 1,800 r with 100 kv., 1 mm. Al total filter and 4 inch (10 cm.) distance. The patient is asked to report for observation in six weeks. If warty tissue still remains, a 40 per cent salicylic acid plaster is applied for a period of four days and the area pared down. Occasionally this method fails and the wart is then treated with liquid oxygen or is surgically removed. At the time of therapy the patient is told that he may have some reaction within two weeks following treatment and that approximately four weeks lapse before the reaction subsides. The patient is also advised that should this treatment fail to produce a cure, the area is not to be irradiated again.

Of 80 patients in our group we were able to follow 58 persons for an average period of 84.3 months. Most of these patients, 47, received only a single dose of radiation averaging 1,700 r. There were 33 patients who were given fractional radiation treatments, averaging 2,200 r within an eight day interval.

The distribution of warts treated is shown in Table 1. The majority of plantar warts occurred on the ball of the foot. The average follow-up period was five years.

TABLE I

DISTRIBUTION OF WARTS TREATED

	Total	Per Cent
Ball of Foot	59	67.9
Mid Foot	7	8.6
Toes	8	9.9
Heel	8	9.9
Side of Foot	3	3.7

SUMMARY

Radiation therapy, if the proper requirements are followed, is the treatment of choice for plantar warts. We obtained the following results: Cured with disappearance of wart, 60 or 75 per cent; cured with some callus formation, 12 or 14.8 per cent; no effect or recurrence, 8 or 9.9 per cent; post-irradiation damage, 0 or 0 per cent.

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A SCINTILLATION CRYSTAL ROENTGEN-RAY DOSIMETER*

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IN ORDER to design or evaluate an experimental determination of the dose distribution resulting from roentgen irradiation, it is necessary to have a clear picture of the physical processes occurring in the medium. The roentgen-ray beam must be considered to consist of discrete particle-like photons. The possible interactions between a roentgen-ray beam in the million electron volt energy range and a material medium result in the complete removal of a primary photon and the production of secondary particles which can be some combination of lower energy photons, electrons or positrons. However, a completely negligible amount of the energy of the photon is delivered to the medium in the primary ionization process. It is the secondary products which actually distribute the energy through the medium. Consider a 1 mev. photon which is absorbed in a medium. An amount of energy of 1 million electron volts is removed from the primary beam but this energy is actually delivered in the form of 30,000 or so separate exciting or ionizing encounters between the secondary products and the atoms and molecules of the medium. It is these excitations and ionizations involving small amounts of energy and occurring at some distance from the primary absorption event which produce biological effects.

To have biological significance, then, a measurement of the dose distribution resulting from the passage of a high energy roentgen-ray beam through matter should be in terms of the energy per unit volume actually delivered to the medium in these low energy encounters. The result of such a measurement is called the energy dose distribution. To point out an extreme example, a measurement of the distribution of the primary roentgen-ray beam in the medium would have no direct biological significance. A further requirement on a dose measurement is that it not disturb the dose distribution which would exist in the absence of the measuring instrument. Since it is impractical to measure the dose directly in the medium a foreign body of some sort has to be introduced. Conventionally this is an air volume surrounded by a suitable wall or a photographic emulsion. In both cases it is the ionization produced in the foreign body by the secondary products which is measured and as long as the energy of these secondary particles is not too high this ionization is a good indication of the energy dose in the medium. However, there is good evidence indicating that as the energy of the secondary products approaches the million electron volt range the relation between the ionization in the foreign body and the energy dose in the medium becomes dependent on the energy of the ionizing particles. This energy dependence could be determined for any particular instrument but this does not improve matters since the energy distribution of the secondary ionizing particles varies in an unpredictable way throughout a material medium.

Consider for a moment a small organic scintillation crystal immersed in a biologically equivalent material such as water. The electron stopping power of the crystal will be very nearly equal to that of water over a very large range of energies. If there are secondary electrons passing through the water and the crystal their energy loss in the crystal will be the same as the energy which they would lose in an equal volume

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of water at the same position. This energy which the electrons lose to the crystal results in an amount of light output which is proportional to the energy loss. Furthermore, the roentgen-ray absorption in the crystal will be the same as that in water so that the introduction of the crystal will not disturb the energy dose distribution in the rest of the medium. A measurement of the light output of this crystal would seem to be a very satisfactory way of determining the energy dose in the medium. Such a scintillation crystal dosimeter has been built and used to measure the energy dose distribution in a water phantom exposed to the roentgen-ray beam from the Case betatron.

DESCRIPTION OF CRYSTAL PROBE AND ASSOCIATED EQUIPMENT

The fundamental component of the dosimeter is a cube of anthracene $\frac{3}{8}$ inch on an edge. The light output of the crystal is conducted to the photocathode of a 931-A photomultiplier through a lucite light pipe. Since the dosimeter is to be immersed in water, total internal reflection cannot be used so the light pipe and crystal were covered with an aluminum mirror surface and a protective layer of silicon monoxide. These layers were thermally deposited in vacuum and were on the order of 4×10^{-6} in. thick. The light collecting efficiency of this system is very good.

Figure 1 is a photograph of the scintillation crystal probe. The photomultiplier tube (931-A or 1P21) and dynode voltage divider are enclosed in a soft iron shield. The anthracene crystal can be seen on the end of the lucite rod.

The integrated output of the photomultiplier is on the order of 0.01 microamperes and can therefore be amplified by a very simple D. C. amplifier having as small a time constant as desired. This offers a very definite practical advantage over the very long time constants which are unavoidable when using the small current techniques required with air chamber dosimetry. In order to eliminate the effect of variations in the intensity of the roentgen-ray beam all data were taken in the form of the ratio between the doses measured with a probe in the phantom and with a fixed monitor. The monitor was simply an anthracene crystal

FIG. 1. Scintillation crystal probe.

cemented directly to the envelope of another 931-A photomultiplier. The signal from the monitor went to an exactly similar amplifier and the ratio of the outputs of these amplifiers was read directly from a ratiometer.

The depth dose was measured in a cubical lucite box having inside dimensions of 20 in. filled with water. A 10 in. diameter window of 5 mm. aluminum was provided for the entrance of the beam. The measuring probe was mounted on a carriage which moved on rails along a bridge spanning the tank. The bridge moved on rails along the side of the tank. The position of the probe could thus be varied along the beam and perpendicular to it in a horizontal plane. The position could be controlled to within 0.01 in. by selsyn motors mounted on the tank and selsyn generators in the betatron control room. Measurements along the axis of the beam required accurate alignment of the tank which was achieved by using a surveyor's transit whose position on the axis of the beam was checked photographically.

The source of roentgen rays was the Case flux-forced field-biased betatron.[1] The peak energy could be controlled by varying the D.C. field bias and the time of expansion of the electron orbit. The peak energy was indicated on a mev. meter which integrated the field during the time of flight of the electrons. The mev. meter was calibrated against well known (γ,n) thresholds. The size of the field is determined by tapered lead plugs inserted in a 4 in. lead shield in front of the betatron and is expressed in terms of the width in centimeters of the geometrically determined beam at a distance of 1 meter from the target.

In order to compare energy dose measurements obtained with the crystal dosimeter and

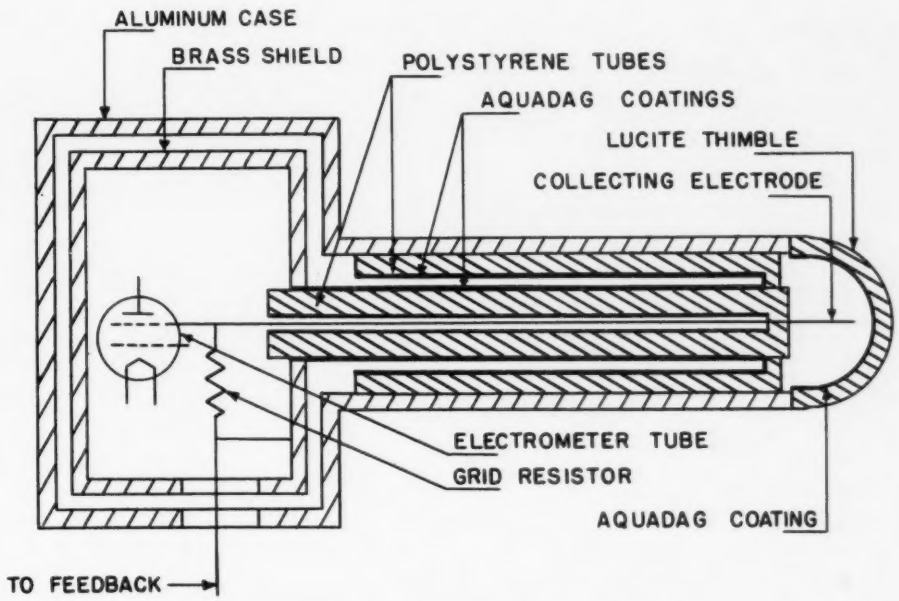

FIG. 2. Air ionization chamber probe showing guard electrode details.

with a conventional air chamber, two air ionization chamber probes and D. C. amplifiers were built, similar to those used by Johns *et al.* at the University of Saskatchewan.[2] The chamber walls and central collecting electrode were made of lucite and graphite respectively in order to keep the electron stopping power and the roentgen-ray absorption coefficients of the chamber as near to those of water as possible. The electrometer pre-amplifier was separated from the air chamber by about 10 in. and connected to it by a stem consisting of three concentric tubes. The outermost was aluminum and provided mechanical strength as well as an electrical connection between an aquadag (colloidal graphite) coating on the inside of the chamber wall and ground in the amplifier. The other two tubes were polystyrene. A fine copper wire passing through the innermost tube connected the collecting electrode to the grid of the electrometer tube. An aquadag coating on the adjacent surfaces of the polystyrene tubes was connected to a brass shield around the electrometer tube and to the feedback end of the electrometer grid resistor. The voltage across this resistor is several millivolts and practically constant. The electrometer grid circuit is thus electrically shielded by a guard electrode at grid potential and any polarization of the polystyrene due to roentgen rays will not result in current in the grid circuit. The sensitivity of the stem when exposed to the direct roentgen-ray beam was found to be well under 0.5 per cent of that of the air chamber itself over a wide range of energies. A schematic diagram of this guard electrode air chamber probe is shown in Figure 2.

RESULTS OF DEPTH DOSE STUDIES

All data obtained from a particular run were plotted as the logarithm of the measured ratio between probe and monitor against the depth. Although changes in the position of the monitor or any of the other operating conditions between runs would change the ratios obtained, a simple translation would suffice to normalize the resulting depth dose curves. A justification of this technique was obtained by comparing the normalized data obtained from runs in which the only difference was the location of the monitor or the average intensity of the beam. In all such cases the data points from the different runs with the scintillation crystal probe differed by less than 1 per cent. The results of two such comparisons are shown in Figure 3. The consistent difference exhibited in one comparison at depths greater than 8 in. was caused by a shift in the zero balance of one of the amplifiers.

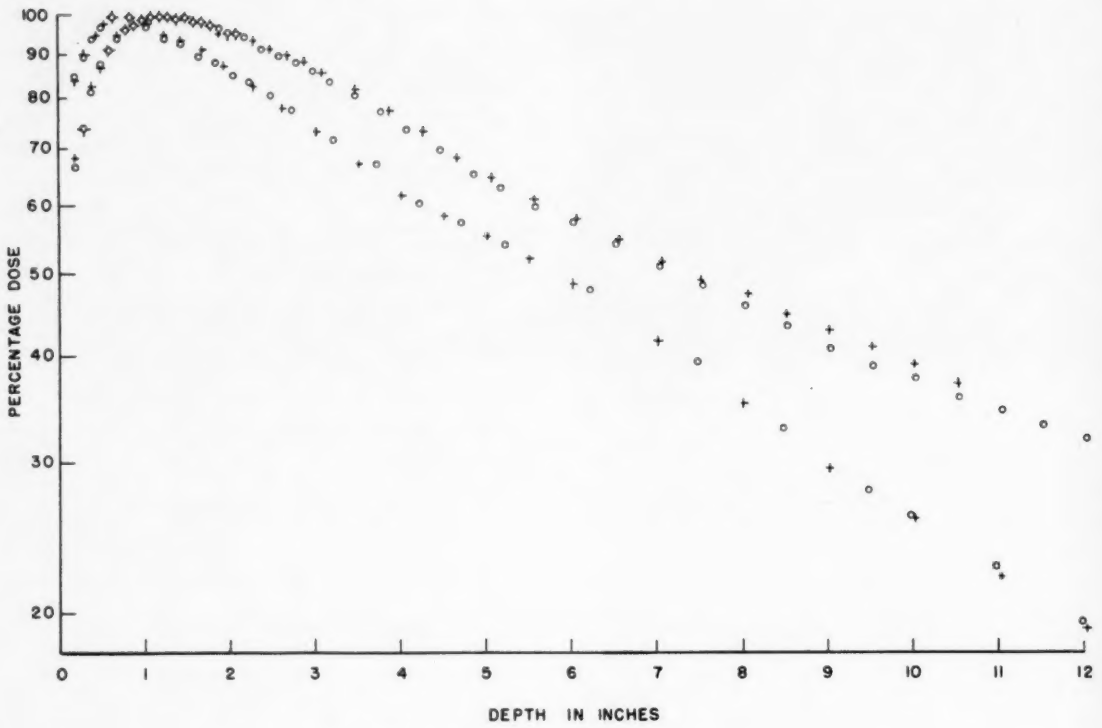

FIG. 3. Typical depth dose curves.

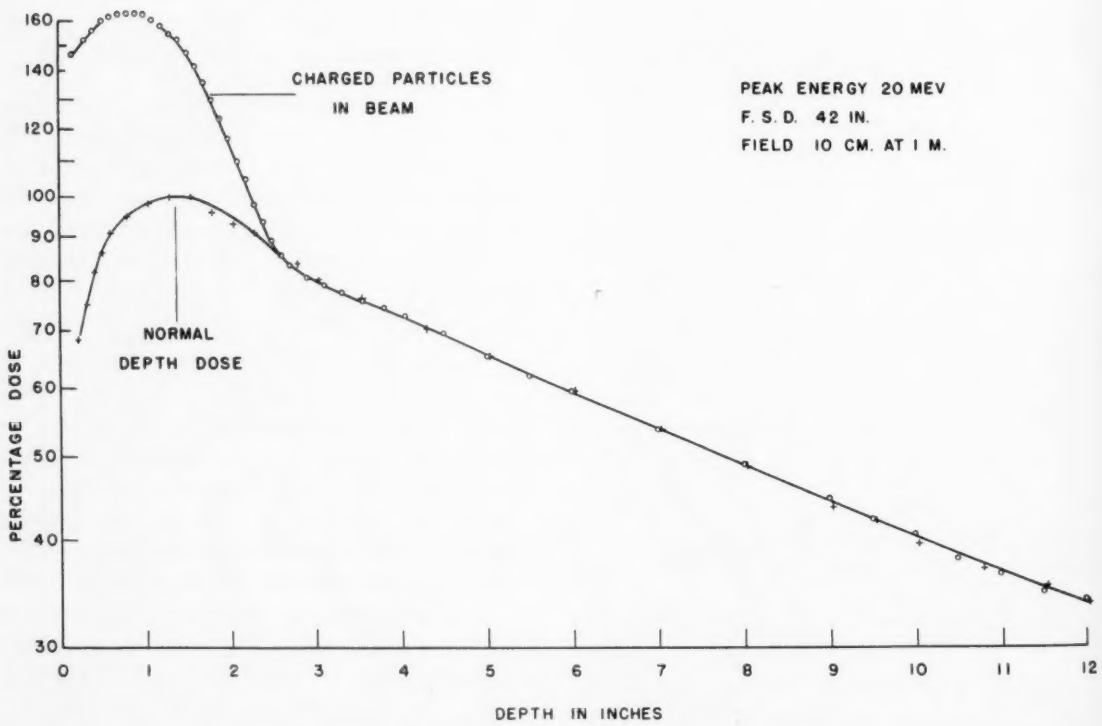

FIG. 4. The effect of charged particles on the depth dose.

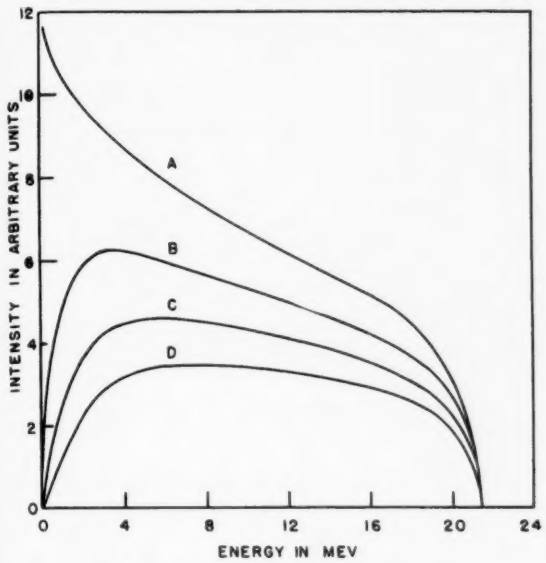

FIG. 5. Modifications to roentgen-ray spectrum due to absorption in water. Curve A is the Schiff distribution while curves B, C and D represent the modification of the primary spectrum due to absorption in successive 10 cm. layers of water.

The first depth dose curves actually obtained exhibited a very pronounced peak at small depths (see the upper curve in Fig. 4). This was attributed to the presence of electrons in the incident beam. The peak was removed by placing a magnetic field of 800 oersteds over the beam as it emerged from the collimator. The "normal depth dose" curve in Figure 4 was obtained in this way.

The depth dose at depths beyond 3 or 4 in. decreases approximately exponentially. This results from the filtering action of the medium. The roentgen-ray absorption coefficient for water decreases rapidly up to about 1 mev. and then is roughly constant to above 100 mev. The low energy end of the roentgen-ray spectrum will thus be filtered out by a relatively thin layer of water leaving a band of energies with essentially constant intensity. The absorption in further layers is approximately the same for all of the energies which are left. This effect is illustrated in Figure 5 where curve A is the distribution of roentgen-ray intensity in the forward direction from a thick molybdenum target and the other

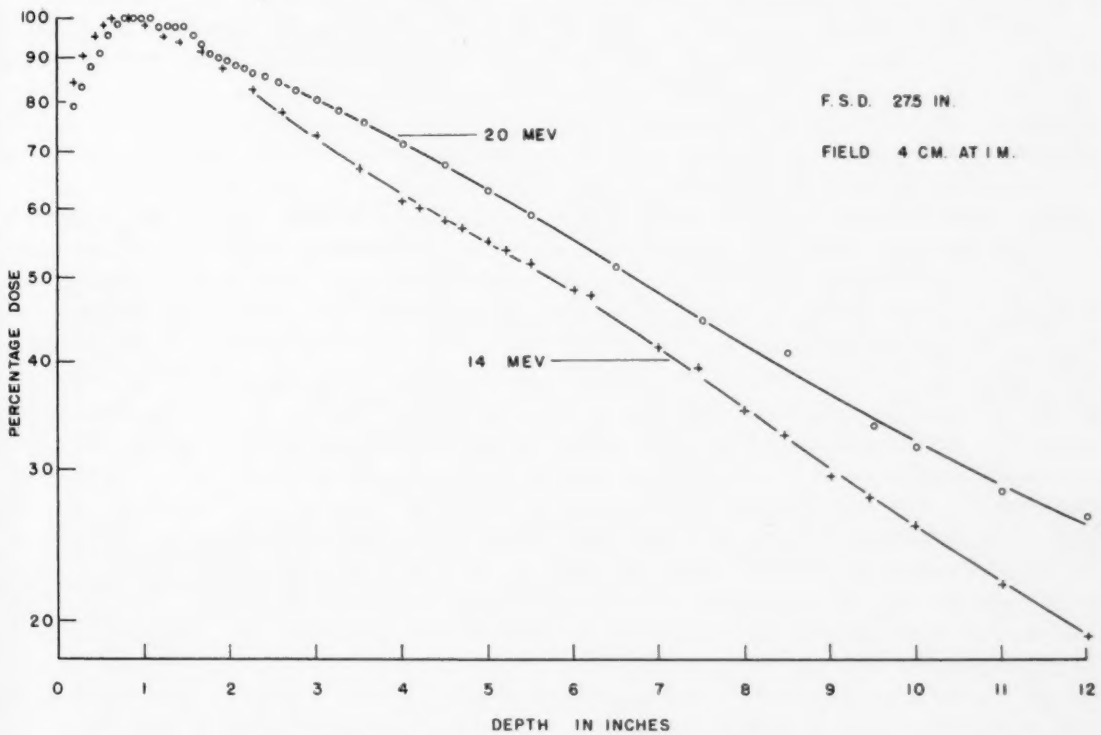

FIG. 6. Dependence of the depth dose on peak energy.

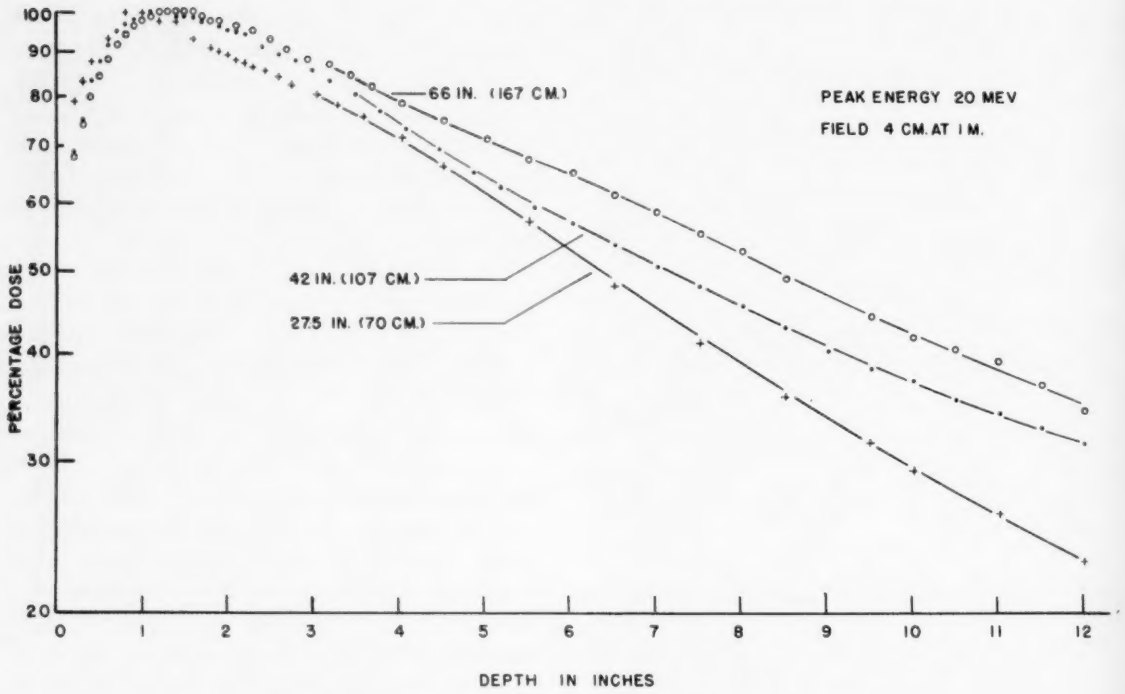

FIG. 7. Dependence of the depth dose on focal skin distance.

curves represent the effect of successive thicknesses of 10 cm. of water. The roentgen-ray flux is not measured but the energy dose will approach equilibrium with the roentgen-ray flux once the roentgen-ray spectrum becomes nearly constant. Thus the energy dose will decrease approximately exponentially as the roentgen rays are exponentially absorbed. On a logarithmic depth dose plot this will appear as a roughly straight line. The slope of this line will vary only slightly with the peak energy of the roentgen-ray spectrum but will depend upon the focal skin distance (from the roentgen-ray source to the surface of the medium) and in certain ranges upon the field size. Figure 6 shows the dependence of the depth dose on peak energy. The dependence upon the focal skin distance is shown in Figure 7. The principal effect here is simply the difference in the inverse square of the distance to the source. If this were the only effect, removing the inverse square dependence should lead to the same slope for all three curves. The result of making this correction to the data of Figure 7 is shown in Table 1.

No great amount of significance is attached to these results since the shape of the depth dose curve was also found to depend upon field size and changing the focal skin distance effectively changed the field size even though the same collimator was used.

The effect of field size on the depth dose is understandable in terms of the long ranges of the secondaries at high energies. Although the secondaries are concentrated in the forward direction there will be a significant contribution to the dose on the axis from secondaries scattered through large angles from points as far from the

TABLE I

Focal Skin Distance	Effective Absorption Coefficient after Removing the Inverse Square Dependence
66 in.	2.79×10^{-2} cm.$^{-1}$
42 in.	2.87×10^{-2} cm.$^{-1}$
27.5 in.	2.85×10^{-2} cm.$^{-1}$

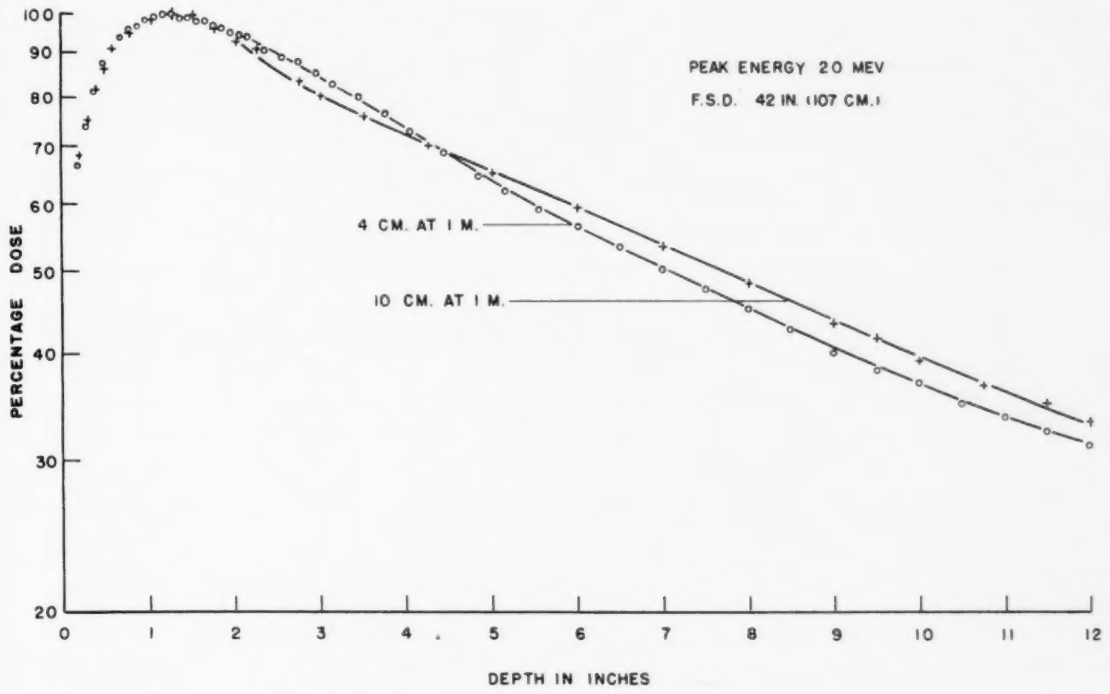

FIG. 8. The effect of field size on the depth dose.

axis as their maximum range. Narrowing the beam to a radius less than this range will thus reduce the dose at the crystal. An attempt to predict the actual shape of a depth dose curve in these terms is complicated by the change in the energy distribution of the secondaries as a function of depth. Figure 8 illustrates the effect of field size on the depth dose. A measurement of the variation in dose normal to the beam indicated a continuous change in dose at the geometrical edge of the beam and a dose which was still on the order of 20 per cent of that at the center of the beam after moving half of a beam width beyond the geometrical edge. This is in qualitative agreement with the explanation offered above. No particular significance is attached to the fact that the curves cross since this results from the arbitrary normalization at the depth of maximum dose. It seems reasonable to expect that, in terms of the absolute dose, the curve obtained with the larger field would never fall below the curve obtained with the smaller field.

Data obtained under the same operating conditions with the crystal probe and with the air chamber are shown in Figure 9. That the shapes of the curves at small depths and the depths at which the maximum dose occurs differ is not suprising since it is in this region that the energy distribution of the secondaries is changing rapidly and measurements with an energy sensitive detector would be expected to differ from the true energy dose. That the curves agree well at large depths is also to be expected since here the energy distribution of the secondaries is changing very slowly and the energy dependence of the detector is unimportant.

One of the important advantages in the use of high energy roentgen rays for therapy is the decrease in the energy absorbed in bone.[4] At low energies the absorption coefficient of bone is considerably higher than that of tissue and the dose which can be administered to tissue is severely limited by the much higher dose which is being received by bones and the tissue directly behind them. However, from 0.1 mev. to 5 mev. the absorption coefficients of bone,

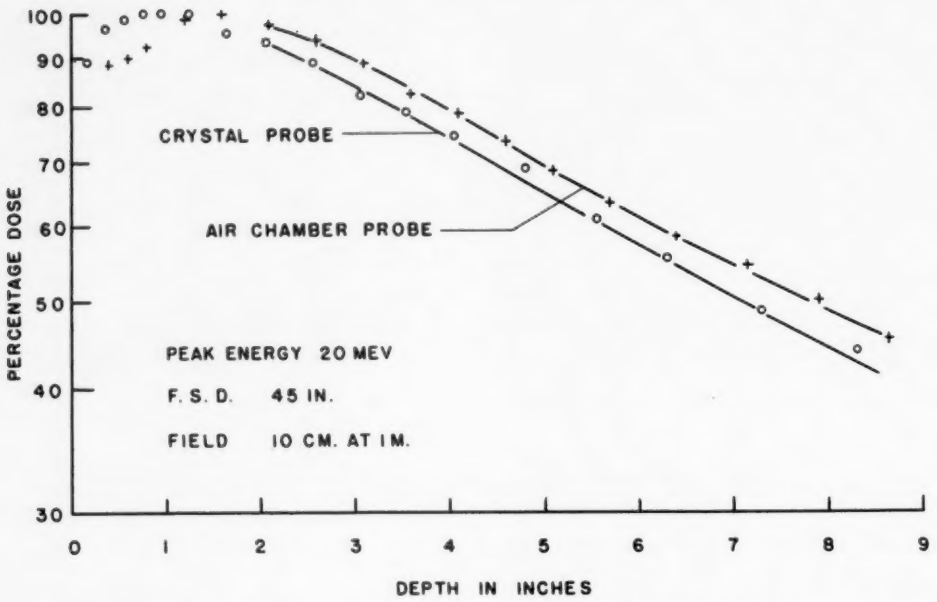

FIG. 9. Comparison of air chamber and scintillation crystal probes.

muscle, fat, air and water are equal and the presence of bone in a volume of tissue to be irradiated with roentgen rays in this energy range would not limit the tissue dose which could be administered. A check on this effect was made by measuring the depth dose when a human femur was placed in the water. In Figure 10 the data obtained in this way are displayed along with a normal depth dose curve. The results are in agreement with predictions by Laughlin.[4] By way of contrast the data obtained when a $\frac{1}{8}$ in. sheet of lead was placed in the same position as the femur are also shown. In this case the dose was increased by nearly 20 per cent on either side of the lead. Of particular interest is the large dose in front of the lead resulting from back-scattered secondary radiation.

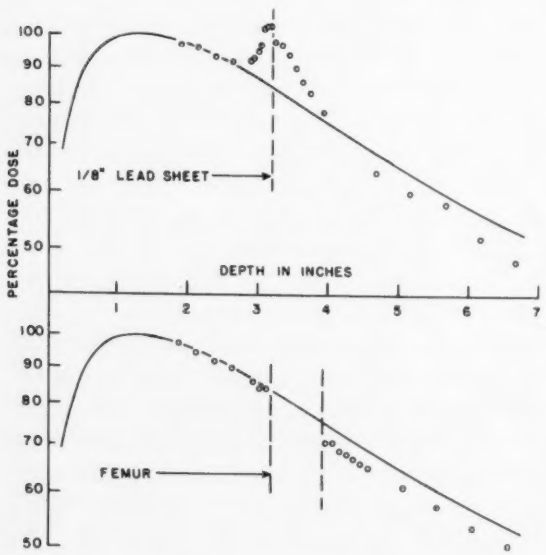

FIG. 10. The effect of inhomogeneities on the depth dose.

A smaller crystal probe using a $\frac{1}{8}$ in. cube of anthracene was constructed in order to check the energy dose distribution in more detail. Sufficient data were obtained to show that nothing new could be learned in this way. The dose could be measured at slightly smaller depths but was not reduced appreciably. Placing the crystal against the window but on the air side gave a dose 40 per cent of that at the maximum. A correction to the depth to allow for the aluminum window can be made and the dose extrapolated to zero depth. This extrapolation can be done in several ways but no reasonable method leads to doses at zero depth which are less than 50 per cent of the maximum. The dose observed in front of the window is quite

reasonable for a crystal with finite thickness. It might be expected to be slightly less than the dose extrapolated to zero depth since large angle scattering from the body of the water is greatly reduced. A rough check was made on the contribution of backscattering to the dose measured directly in front of the phantom. Using a block of ice in place of the water phantom, the dose was measured with and without the phantom. These indicated a contribution of about 5 per cent to the dose at this point. This would be expected to be slightly higher with the aluminum window and water. Unpublished data obtained in this laboratory using a liquid scintillator directly as a phantom indicate that the entrance dose is not less than 40 per cent of the maximum.

This investigation offers some clues to possible reasons for the difficulty encountered in comparing dose distributions obtained from different experiments.[3,5] The depth dose relation appears to be more complex than previously supposed. For instance, in no case was a depth dose curve obtained which failed to exhibit several changes in the sign of the curvature at depths greater than that of the maximum dose. The high degree of reproducibility of the data precludes attributing this to fluctuations in the measuring equipment. Performing some smoothing process (such as obtaining fewer data or fitting an exponential curve to the data) could distort the curves badly. Furthermore, the effects of charged particles in the primary beam and of variation of peak energy, focal skin distance and field size would seem to make it impossible to compare data obtained under slightly different conditions even if all of the conditions were known exactly.

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OBSERVATIONS ON GROWTH RATES OF HUMAN TUMORS*

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THE definition of cancer, its diagnosis and its prognosis all depend upon description of growth. To the layman a synonym for cancer is a "growth." There are no quantitative terms for the description of growth or growth rate in clinical use. There has been no attempt to assign values that would define "rapidly" or "slowly" growing. Estimates of growth potentiality are implied in the descriptive phrases "poorly differentiated" or "well differentiated," "highly malignant" or "low grade malignancy," and in systems of grading. These qualifying terms represent a personal impression, clinically useful in prognosis, but relative in nature. They do not lend themselves to uniform application or precise measurement for purposes of comparison.

This study is an attempt to evolve a method of measurement of growth rate having clinical application for human tumors and to test its usefulness against observed phenomena.

Growth is related to size and time. The diagnosis of cancer is made when it reaches a certain size and when it has been present for a certain length of time. The value of the diagnosis lies in the implied prognosis which, if meaningful, predicts in a general way the amount of growth that will take place in a given period of time. For a diagnosis of malignant melanoma, the prognosis and prediction is that typically it will reach a total volume of tumor which will cause the patient's death in a short period of time due to a rapid rate of growth. For leiomyoma the prediction is that this will increase very little in size over a long period of time due to a slow rate of growth. The usefulness of pathologic diagnoses vouches for the consistency of the growth behavior of recognized types of tumor.

Whereas the limited evidence available at the time of diagnosis is used to predict the future course of the disease, this study utilizes observations made throughout the clinical course of the disease to determine behavior in the period prior to diagnosis.

HYPOTHESIS

The volume of tumor depends upon the duration of the period of growth and the rate of growth. If the time interval and change in volume are known, the average growth rate can be determined. If the growth rate is determined, and assumed to be constant, the duration of a given tumor and the time of inception can be estimated.

The commonest concept of the origin of cancer is that as a result of a mutation involving a single cell, succeeding divisions of cells establish a colony with characteristics recognizable as cancer. The original mutation could never be effective if the involved cell did not divide, and the cancer colony could not grow without cell division. The simplest view of cell growth is that one divides to become two, and each of these divides to become four, eight, sixteen, etc. If the growth rate of the hypothetical tumor were constant it could be described in terms of "doubling time," as half time describes the decay of a radioactive isotope. The assumption of a constant growth rate is the basis for the simplest hypothesis as to the possible duration of cancer.

According to this hypothesis a single cancer cell 10 μ in diameter will grow to a nodule 1 mm. in diameter in 20 doublings (Fig. 1 and 2). This is taken as the dividing

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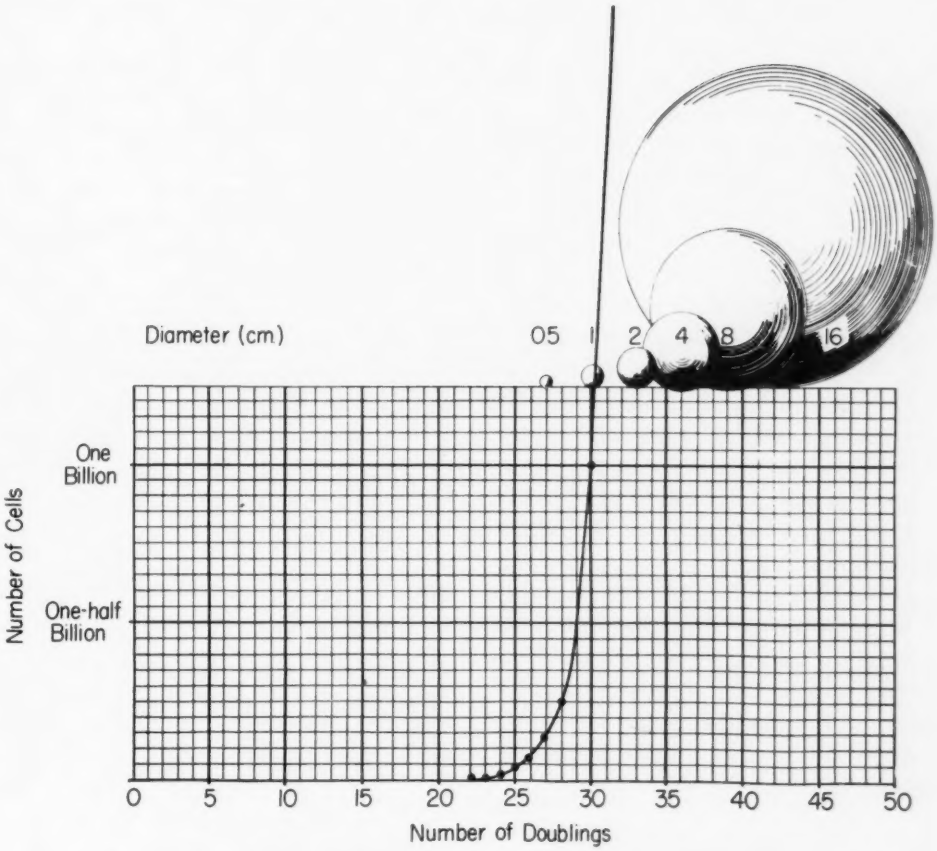

FIG. 1. Growth curve of hypothetical tumor on arithmetic coordinates.

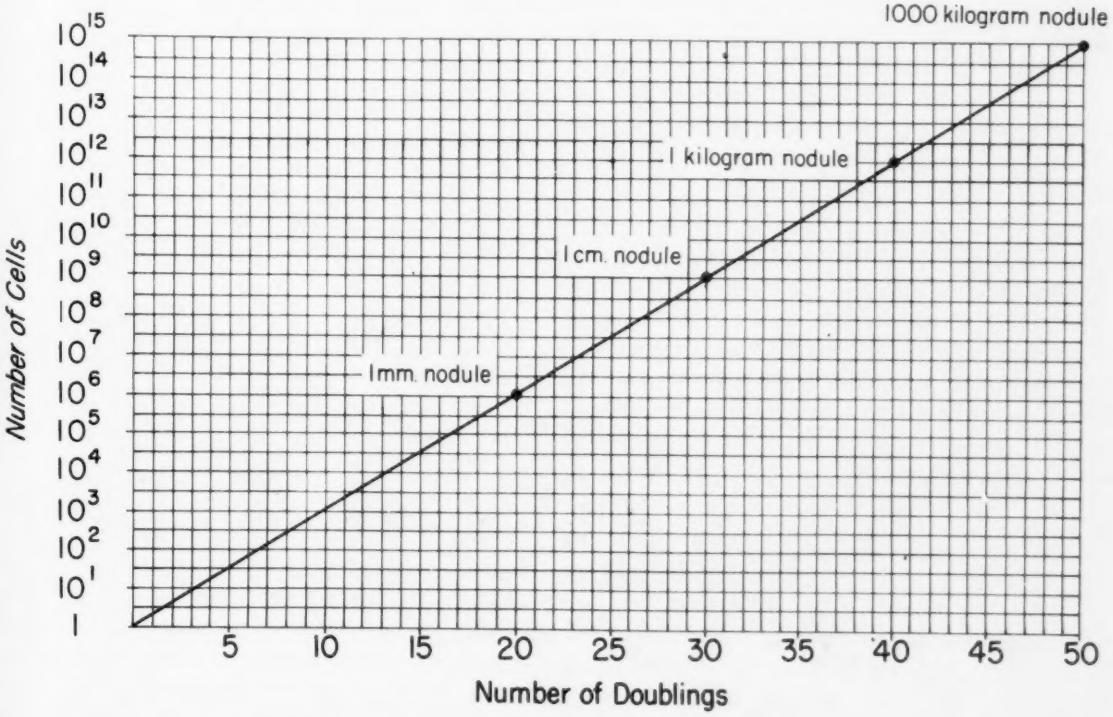

FIG. 2. Growth curve of same hypothetical tumor on semilogarithmic scale.

line between undetected growth and the minimal lesion that could be detected by a sign or symptom. A 1 cm. nodule, a likely size for early diagnosis, would be achieved in 30 doublings. A further ten doublings will produce approximately one kilogram of cancer tissue. The patient may live beyond this point but the disease is approaching termination because another five doublings of tumor volume will equal half the weight of a 70 kilogram man. Thus, the total maximum duration of cancer is of the order of time required for 40 doublings in volume and half of this occurs in a period of undetected growth prior to the earliest possible sign of symptom.

Evidence which is required is (1) knowledge of the range of doubling times for human cancer, and (2) information on whether the manner and rate of growth of individual tumors is sufficiently characteristic to bear out prediction based on this hypothesis.

OBSERVATIONS ON PULMONARY METASTASES

In the clinical phase of tumor growth the primary lesion is often removed very shortly after diagnosis and no increase in size is evident or measurable in this short interval. If the lesion is successfully removed, there is no recurrence and no material is available for estimating rate of growth. There is, however, ample opportunity for observations on persistent and growing tumor in uncured patients. Pulmonary metastases particularly lend themselves to observations on growth since the roentgenogram forms a permanent record and measurements can be made at successive intervals.

The growth rate is expressed as doubling time. This is determined from calculated volumes of a given pulmonary metastasis at successive observations, at known intervals of time. The determination of doubling time has been simplified by the use of graph paper designed for this purpose (Fig. 3).

Observations on the growth of pulmonary metastases in 24 patients led to an estimate of the range of growth rate in human tumors, and of the possible duration of pulmonary metastases (Table 1).

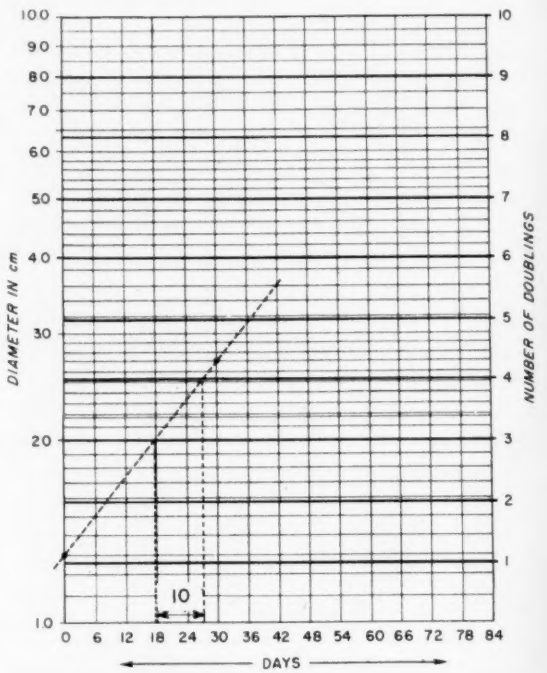

FIG. 3. Chart for estimating doubling time directly from measured diameter of nodules. This graph paper is based on the logarithm of the cube root. The heavy, evenly spaced lines represent successive doublings in volume. The procedure is as follows: (a) The diameter of the pulmonary metastasis at the first observation is plotted on *0* vertical axis. The diameter of the same nodule at the second observation is plotted on vertical line appropriate to the interval in days between the first and second observation; (b) draw straight line between plotted diameters; (c) where this line crosses any two heavy lines indicating doubling, drop two verticals to the base line; (d) the horizontal distance between these two vertical lines represents the doubling time in days.

Growth rates in this group of patients ranged from a doubling time of 11 days to 164 days. There is an element of selection in that the particular types of tumors included are those which tend to produce sharply defined metastatic nodules in the lung. Other lesions such as carcinoma of the lung or metastasis from breast cancer less often present as discrete nodules for satisfactory measurements. Based on these

TABLE I

GROWTH RATES OF PULMONARY METASTASES IN 24 PATIENTS

Diagnosis	Doubling Time, Da.	Estimated Duration of Pulmonary Metastases When First Seen		
		yr.	mo.	
1. Teratocarcinoma of testis	11	1	1	
2. Embryonal carcinoma of testis	11		9	
3. Embryonal carcinoma of testis	13	1	1	
4. Ewing's tumor	17	1	5	Rapidly growing tumors
5. Angiosarcoma	21	2	8	Doubling time up to 25 days
6. Embryonal carcinoma of testis	21	2	1	
7. Seminoma of testis	22	1	9	
8. Teratoma of testis	25	2	1	
9. Adenocarcinoma of breast	28	2	6	
10. Carcinoma of testis	30	2	7	
11. Carcinoma of larynx	37	2	7	
12. Embryonal carcinoma of testis	40	3	4	Intermediate growth rates
13. Wilms' tumor	43	3	8	Doubling time 25–75 days
14. Carcinoma of rectum	49	3	11	
15. Carcinoma of cervix	58	5	2	
16. Carcinoma of rectum	73	6	5	
17. Carcinoma of breast	84	8	4	
18. Carcinoma of rectum	91	6	7	
19. Carcinoma of rectum	123	11	5	Slowly growing tumors
20. Synovioma	128	11	6	Doubling time 75 days and over
21. Baso-squamous cell carcinoma of skin	131	10	9	
22. Squamous cell carcinoma of lip	143	13	5	
23. Carcinoma of testis	153	14	6	
24. Carcinoma of esophagus	164	14	9	

growth rates and the size of the pulmonary metastases when first seen, the time of establishment of the pulmonary metastasis is estimated. In all but one instance the time of inception of the metastasis falls prior to the earliest sign or symptom of the primary disease.

REPORT OF A CASE

CASE NO. 20. T.S. was twenty-nine years old in 1946 when the first episode in his history occurred. He was on maneuvers in Italy and injured his knee in a fall into a foxhole. Then, for the first time, he noticed an acorn-sized nodule behind his left knee. The knee was stiff for a few days and then gave him no further trouble. The nodule gradually increased in size but it was not until June, 1950 that he sought medical attention. The mass in the left popliteal space was about 15 cm. in diameter, but even then was asymptomatic. A biopsy was performed and the diagnosis reported as synovioma. Roentgen examination of the chest showed no metastases. Amputation was advised but refused. In November, 1950 he returned to the hospital because of pain in the knee and ulceration of the overlying skin. He now consented to amputation, but re-examination of the chest showed a minute metastasis. The opinion was expressed that, "the patient had signed his own death warrant by refusing amputation six months earlier." Nevertheless amputation was performed and the patient was followed until the time of death some 35 months later.

Comment. Two interpretations may be placed upon the course of this patient's disease.

1. This is the commonplace story of the patient with a diagnosis of sarcoma. The primary lesion has been evident for many years and grows so slowly as to appear innocuous. Treatment is often deferred until a mass of appreciable size is present. Despite the long history of a slowly growing mass, it often appears that about the time a patient seeks medical attention the tumor suddenly begins to grow more rapidly. It is commonly appreciated that the chance for cure depends on early diagnosis and treatment. Even so, it is very difficult to be optimistic because we often find recurrences and metastases developing months or years after apparently successful treatment. Persistent disease or distant metastases may lie dormant for long periods of time and then suddenly, under the influence of some unknown accelerating factor, metastases begin to grow wildly in many sites and the patient pursues a rapid downhill course.

2. The second interpretation is based upon the evidence that this tumor has a relatively constant doubling time of 128 days (Table II). Assuming a constant growth rate during the silent phase of the pulmonary metastases the original metastatic cell or metastatic embolus reached the lung approximately eleven years before it was first identified and seven years before the popliteal nodule was first noted. Assuming the acorn-sized nodule discovered in 1946 to be a centimeter in diameter, this sarcoma had already been present for about eleven years, and during this interval had already exercised its ability to metastasize. This being the case, the delay of amputation from June, 1950 to November, 1950 was in no way harmful to the patient. In fact it gave him the use of his limb for several additional months. Amputation was justified in the end to control local disease which was becoming incapacitating. Nothing more could be done by way of intervention for this patient since the outcome was established before the patient was even aware of his disease. It would have been of no avail to have amputated his leg even in 1946 had the diagnosis been established at the time when he fell into a foxhole. Metastases were already present (Fig. 4). Local removal at the time might have effected local control and thus prevented eventual amputation. Diagnosis of synovioma and radical treatment at the time of the first sign or symptom would only have deprived the patient of his leg may years earlier.

TABLE II

OBSERVATIONS ON GROWTH RATE OF PULMONARY METASTASIS IN CASE NO. 20

Date	Diameter (cm.)	Interval (days)	Doubling Time (days)
11/ 7/50	1.6		
5/ 1/51	2.2	175	126
11/20/51	3.4	204	109
7/14/52	4.9	241	152
10/ 9/52	5.9	87	108
1/ 6/53	6.8	88	144
7/ 5/53	9.4	181	130
11/ 7/50–7/ 5/53		976	128

The usefulness of the concept of a doubling time as an index of growth rate hinges upon whether evidence can be obtained that such a value is a characteristic of a tumor governing its behavior throughout its entire duration.

OBSERVATIONS ON WILMS' TUMORS

If doubling time is a meaningful characteristic of any tumor, this should govern the time of the appearance of the primary lesion if any limits could be placed upon the time of inception. It should also govern the time of recurrence following surgical removal if the patient is not cured.

For tumors of childhood, one limit can be placed upon the possible time of inception; a tumor cannot have been present longer than the age of the child at the time of diagnosis plus the nine months of gestation. A tumor which is discovered at birth must have reached the size of clinical recognition within nine months. If a constant or characteristic growth rate governs the behavior of this tumor, the

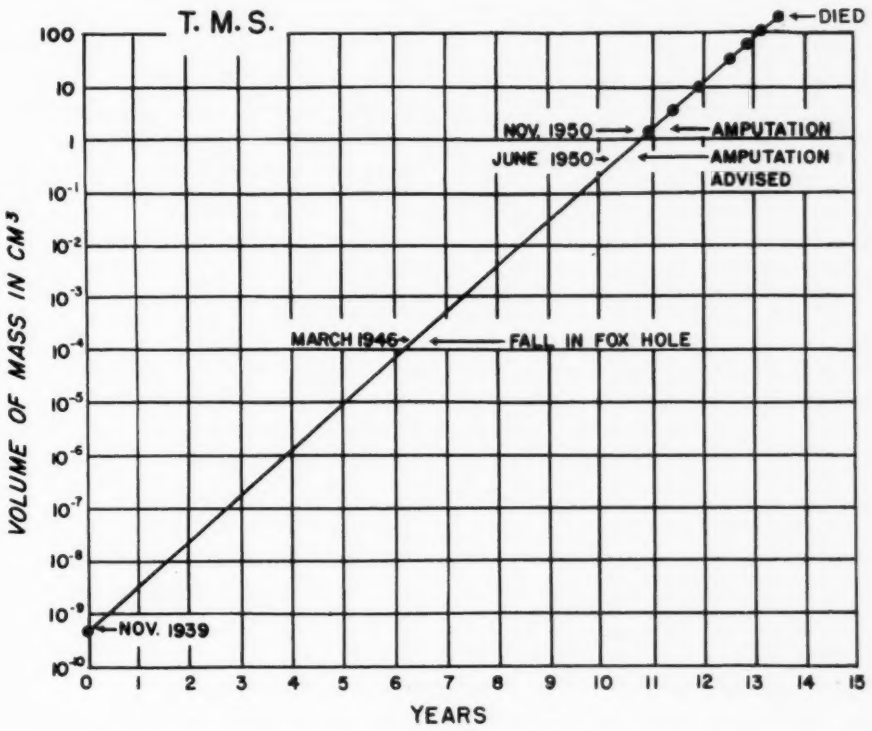

FIG. 4. Estimated duration of pulmonary metastasis in Case No. 20.

recurrence, if it is to develop, should reach a size equal to the primary lesion in a maximum of nine months. In a three month old infant an adequate follow-up period would be twelve months (three months of life plus nine months of gestation). In a five year old, a postoperative period of five years and nine months would be required before the child could be judged free of tumor.

Wilms' tumor was chosen for study because of its relative frequency among childhood tumors and because the criteria for diagnosis are not obscure. The primary lesion has usually reached such a bulk at the time of diagnosis that even the parent recognizes it. A recurrence to equal size is not apt to be overlooked in periodic follow-up examinations.

The information required is simply the age at diagnosis and the age at time of last negative follow-up, first recurrence, or death. A total of 252 histories of children with Wilms' tumor were assembled from published reports and from personal communications with several cooperating physicians and institutions.[5–10,12–14,16,17,19–22,24,26] Of these cases, adequate data for study could be obtained in 206 cases. In the remainder, follow-up was incomplete, the child died immediately after operation, was not treated or adequate information was not available on the time of recurrence of the tumor or death of the child. No effort was made to insure that only "representative" series of patients were included; some series may not include all patients seen by the reporting authors. No attempt was made to select a particular method of treatment; most were treated by surgery or by combined techniques, a few by radiation alone. These factors are unimportant to the hypothesis of uniform growth rate and criterion of cure to be tested. In the absence of such safeguards for uniformity of data with regard to age incidence or treatment, the readers are cautioned to accept derived data on prognosis and curability with appropriate reserve since they are not necessarily typical of all pa-

tients with this disease or present methods of treatment.

The data on age at diagnosis or operation, age at last symptom free follow-up, first recurrence or death are shown in Figure 5 for the 206 usable cases. The first diagonal line represents the time of operation. The second diagonal line limits a postoperative period which is equal to the age of the child at diagnosis plus nine months gestation. The interval between diagonal lines is the total "period at risk" following treatment in which a recurrence should develop if the growth rate of the tumor is uniform during the period of undetected growth for both the primary lesion and the recurrence.

Twenty patients reported as symptom free fall within the period of risk and hence cannot be accepted as "cures." Forty-nine children survived beyond the period at risk and among these there is no recorded instance of death or recurrence. Before these children can be considered "cured," it is necessary to examine the adequacy of reported follow-up. This is quite variable and was obviously not made in accordance with the present hypothesis. The duration of follow-up in years is shown in Table III.

The typical follow-up (median) for these children (beyond the period of risk) is approximately four years. The total follow-up after treatment is longer but in accordance with our hypothesis this is of little importance.

These data will be perhaps more meaningful if the follow-up for each child beyond the period at risk is expressed as a ratio of the period at risk for that particular child. This has been done in Table IV. From this, the typical (median) follow-up beyond the "period at risk" is approximately $1\frac{1}{4}$ times the duration of the period at risk for that child. Over half of these 49 children surviving symptom free beyond the "period at risk" remained symptom free for at least an equal additional period.

If we tentatively accept these 49 symptom free survivals beyond the period of risk as "cures," then an estimate of the

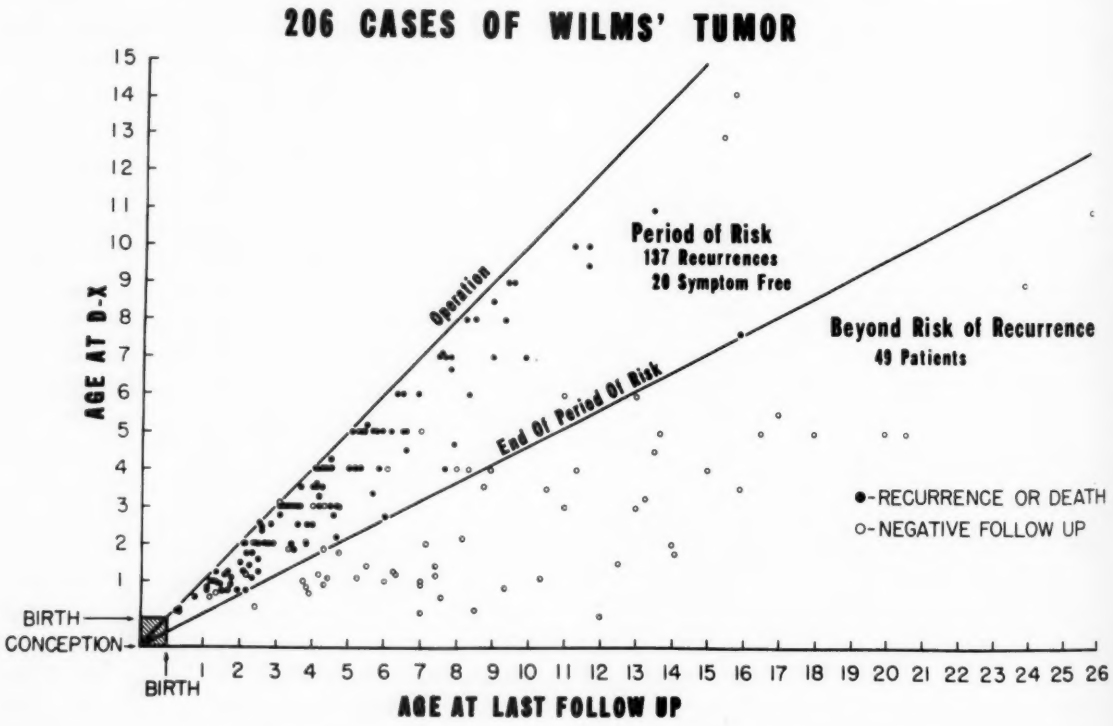

FIG. 5. Recurrences and survivals of 206 cases of Wilms' tumor in relation to predicted period of risk.

TABLE III

DURATION OF FOLLOW-UP IN YEARS BEYOND THE "PERIOD AT RISK" FOR 49 CHILDREN (OF 206) WHO SHOWED NO RECORDED EVIDENCE OF PERSISTENT OR RECURRENT TUMOR AFTER THE END OF "PERIOD AT RISK"

Symptom free years beyond period of risk	0–1.01	1.01–2.0	2.01–3.0	3.01–4.0	4.01–5.0	5.01–6.0	6.01–8.0	8.01–10.0	Over 10 years
Number of children	7	7	6	5	4	5	7	6	2

proportion cured is 49/186 or 26 per cent. Inspection of Figure 5 will show that to designate all one and one-half year survivals, three or five years survivals (after treatment) as "cures" would lead to serious error since recurrences can occur after any of these arbitrary time intervals in individuals of appropriate age.

Boag[3] has proposed a mathematical definition of "proportion cured" of treated cancer patients which may be approximately paraphrased as: "that proportion of the treated group who fail to die in accordance with the pattern of survival time for those patients who die of recurrent or persistent carcinoma." Boag's "maximum likelihood" method of calculation of the proportion cured enables us to calculate the fraction of patients who will ultimately die of the disease and provides the time pattern of their remaining survival. The basic data are given in Table v.

The results of a single calculation are given in Table VI.

It is seen that there is no statistically significant difference between estimates of the proportion cured obtained by the Boag method,[3] or on the basis of uniform growth rate. (The reader is again cautioned to accept the data on median survival after treatment and proportion cured as order of magnitude estimates only, not necessarily typical of present day treatment.)

TABLE V

SUMMARY OF THE STATUS OF PATIENTS INCLUDED IN BOAG CALCULATION OF "PROPORTION CURED"

		Number of Children
1.	Dead of carcinoma	129
2 and 3.	Alive without evidence of carcinoma* (or dead, free of disease)	69
4.	Alive with recurrent or persistent carcinoma	13
	Total	206

* This includes those free of disease who have not reached the end of the "period at risk."

TABLE IV

DURATION OF FOLLOW-UP IN YEARS BEYOND THE "PERIOD OF RISK" EXPRESSED AS A RATIO TO THE PERIOD AT RISK FOR THAT CHILD*

Ratio of symptom free years beyond "period at risk" to the "period at risk" for each child	0–0.49	0.51–1.0	1.01–2.0	2.01–4.0	4.01–6.0	6.01–8.0	Over 8.0
Number of children	7	13	18	4	5	1	1

* Example: An infant is operated at age of 3 months and is found symptom free at age of 33 months. The postoperative period of risk is 12 months (3 months + 9 months gestation). The child is considered to be at risk until age 15 months (age at operation + period of risk). Follow-up period beyond period of risk is 18 months (33 months less 15 months). Ratio tabulated above is:

$$\frac{18 \text{ mo.}}{12 \text{ mo}} = 1.5.$$

TABLE VI

RESULTS OF CALCULATION OF PROPORTION CURED

	Boag Calculation Per Cent	Criteria Proposed Per Cent
Proportion cured	27	26
95 per cent confidence limits*	21–33	20–32

For those dying of carcinoma:
Median survival after treatment—7.5 months
95 per cent confidence limits of median—6.1–9.2 months
Central 95 per cent will die in 0.77–68.2 months

* These define the range of values which would be found in 95 of 100 series of patients of the same size and composition.

The hypothesis of uniform growth rate for a tumor originating in utero represents a conservative basis for criterion of "cure." If the tumor originated in the postnatal period, then it would necessarily have a more rapid growth rate than that postulated in order to become clinically evident. If this same faster rate continued, recurrences from a single residual cell should occur sooner than in the interval, age at diagnosis plus nine months after treatment. The observation that some occur sooner is equivocal information since we know clinically that variable numbers of tumor cells are left behind at treatment. For example, as little as 1 mm. in diameter of tumor nodule left behind at operation would cut the probable time for recurrence to one-half of the period at risk.

The apparent correspondence between the estimates of proportion cured based upon the hypothesis of uniform growth rate and upon the results of the Boag[3] calculation is encouraging. The observed symptom free follow-up interval of our apparent "cures" is reasonable but, in a critical sense, inadequate. These children who were apparently cured would need follow-up to death from other causes and complete necropsy study thereafter to verify rigidly this proposed criterion. The observation that all recurrences reported did fall within the period at risk is considered important. Keiswetter[15] reported experience with treatment of neuroblastoma in childhood, and on application of this method of analysis found all recurrences confined to the period of risk as here defined.

The value of this proposed criterion of cure does not lie in its simplicity alone. As previously indicated, three year or five year symptom free surivival is an inadequate criterion for an individual or a group of patients. The excellent methods of Boag[3] or Berkson and Gage[1] permit the calculation of proportion cured in any series. They provide no method for giving a reliable prognosis for the individual who is treated. If adequately confirmed, this hypothesis may be capable of providing suitable simple criteria for cure of both individuals and groups.

The pattern of recurrence and survival in this series of Wilms' tumor is consistent with the original hypothesis that, for an individual tumor, a characteristic rate of growth controls the time of appearance of both primary lesion and recurrence. The concept of a period at risk, which is equal to the age at diagnosis plus nine months of gestation, provides a clinically useful method predicting the outcome for a given patient.

DISCUSSION

The concept of behavior of cancer that develops with this study emphasizes two aspects that are supported in part by general clinical experience.

1. Observations presented here suggest that a specific rate of growth is a characteristic of an individual tumor. The clinical usefulness of pathologic diagnoses lies in the association of some degree of consistent behavior with morphologic appearance. Assigning a numerical value in the form of doubling time offers a more precise statement of rate of growth than the descriptive phrases "rapidly growing" or "slowly growing."

2. Evidence is added that the duration of cancer before diagnosis may be very long.

We have always been aware that the duration of cancer before diagnosis was too long to permit effective treatment for many patients and this has been the basis of the campaign for early diagnosis. The work of Rigler, O'Loughlin and Tucker,[23] dealing with carcinoma of lung, has greatly extended the known duration of this disease by painstaking search of early roentgenologic records for the minimal roentgen evidence of its presence. Even this does not take into account the still earlier period here referred to as the period of undetected growth.

Consideration of the growth of cancer as a doubling process points to two common illusions as to rate of change.

1. If a 1 cm. nodule is identified on physical examination, or as a pulmonary metastasis in a roentgenogram of the chest, and if at a subsequent examination this nodule has grown to be 2 cm. in diameter, then it is apt to be stated that the nodule has doubled in size. This expression is loosely correct, but the volume of the tumor has increased by a factor of eight. This is attained by three doublings in volume (1–2, 2–4, 4–8) and is a closer approximation of the number of cells involved (Table VII).

2. When the volume of tumor that is doubling at a constant rate is plotted arithmetically, the changing direction of the curves gives the impression of increasing rapidity of growth (Fig. 1). Plotted logarithmically the curve of growth becomes a straight line, reflecting that the rate of change is constant (Fig. 2). Since clinical impressions are based on the behavior of tumors of visible size, our impressions of growth or change in size with time are taken from the slope of the portion of the curve for nodules over 1 mm. in diameter (Fig. 1). If this slope is projected backward as a straight line the impression would be gained of a very recent origin for the cancer. It requires studied consideration of the principles involved to realize that cancer cells could increase undetected at a steady rate for a long period of time and then, without change in rate, appear to burgeon in sudden growth.

These views provide a plausible basis for explaining a number of paradoxical observations on the course of human cancer.

Improvement in cure rates depends upon achieving earlier diagnosis. Although this axiom is often repeated, improvement in cure or survival rate is difficult to recognize. Bloom's[2] series of breast cancers showed that for a duration of symptoms of less than six weeks, three to six months, and over twelve months, the five year survival rates were 50 per cent, 42 per cent, and 52 per cent, respectively. Haagensen and Stout[11] expected the cure rate for cancer of the breast to fall with increasing duration of the disease. They failed to show this correlation and stated they were unable to explain this finding. McDonald,[18] writing of gastric cancer, found that patients with the shortest duration of symptoms prior to treatment had the lowest rate of resectability and the lowest survival rate. The association between a brief duration of symptoms prior to treatment and a low survival rate is attributed to the earlier recognition of rapidly growing tumor as compared with the patient's complacency toward signs or symptoms that develop very slowly. These observations do not disprove the value of early diagnosis; they merely fail to establish it. The long duration of the period of undetected growth of cancer which is suggested here offers an explanation for the failure of early diagnosis to influence cure, survival, or mortality rates.

TABLE VII

THE RELATIONSHIP OF DIAMETER, VOLUME, AND GROWTH IN TERMS OF DOUBLING

	1 Cell	Nodule at First Observation	Nodule at Second Observation
Diameter	10 μ	1 cm.	2 cm.
Relative Volume	10^{-9}	1	8
Doublings	←——30——→	←— 3 —→	
			(1–2)(2–4)(4–8)

It is not early enough by a period of many doubling times equaling months or years.

The late appearance of a distant metastasis after some years of symptom free survival without evidence of persistent disease at the treated primary site, is usually ascribed to dormant tumor cells. Metastases of a tumor having a doubling time of 60 days would require approximately five years to grow from a one-cell stage to a 1 cm. nodule. A doubling time of 100 days would require approximately eight years. It is not necessary to propose that sleeping tumor cells suddenly began to grow. This behavior is compatible with the period of undetected growth for doubling times of the range demonstrated.

It is a frequent clinical observation that a cancer suddenly begins to grow rapidly and a myriad of metastases become evident in a short period of time. Skin metastases of a breast cancer having a doubling time of 30 days would require approximately 600 days or 20 months to develop from a single cell to 1 mm. nodules. Diagnosis and treatment might occur in this period followed by an interval of clinical freedom from disease. If metastases are numerous and unresponsive to treatment, three to six doublings in as many months will be adequate to involve the chest wall extensively. This is apt to receive a clinical appraisal of sudden rapid increase in growth of cancer under some undetermined stimulatory influence. Although there is good evidence that hormonal influences may alter growth rate for some cancers, the simple factor of exponential growth shown in Figure 1 provides an important element in the explanation.

There is an impression, well founded in clinical experience, that cancer in young individuals tends to be rapidly growing and cancer in elderly individuals tends to be slowly growing. This observation is sometimes offered with the suggestion that some vital force present in youth but absent in advanced age is a stimulating factor to the growth of cancer. A simpler explanation may suffice. Doubling times of 60 days and up are considered as moderate to slowly growing. A tumor with a doubling time of 60 days would require about five years to reach the size of a 1 cm. nodule. No tumor growing at this rate can reach this size earlier than an age of four years and three months. Tumors appearing at an earlier age must have a more rapid rate of growth, and their number cannot be diluted by slowly growing tumors which at this age are still in the undetected stage. In the oldest age group, tumors of all growth rates can be present but tumors with the longest doubling time will be discovered only because the individual lived long enough to permit clinical recognition.

The major reservation as to the validity of the hypothesis has to do with the importance of the assumption of a constant growth rate. It must be emphasized first that the assumption of a constant growth rate is the basis for the simplest hypothesis as to the possible duration of cancer. Against this hypothetical behavior, similarities and discrepancies in the behavior of clinical material can be observed and measured.

Brues, *et al.*[4] used a similar approach in studying the relation between latent period and growth rate in chemically induced tumors. They assumed a constant growth rate and an exponential growth curve. Basing growth rate on the proportion of cells in mitosis as representing the hourly increase in tumor size, they calculated the days required for a single cell 10^{-9} cm.^{3} to reach a volume of 1 cm.^{3} They found a high degree of correlation with the actual latent period before the appearance of palpable tumors. They suggested that the growth rate of a tumor in a microscopic stage is important and may be the main factor in determining the latent period in carcinogenesis. The present study on human tumors leads to a similar suggestion.

The essential question is not whether growth rate is constant, but whether the total duration of cancer corresponds to an estimate based upon a constant growth rate. The actual time may be longer or

shorter than indicated. The rate of growth may be rapid initially, slowing in the clinical stages, or it may be slow to start and grow with increased speed in a later stage. It might be expected to follow the familiar sigmoid curve as in bacterial cultures. If growth rate in the period of undetected growth is faster than calculated, then the total duration is shorter than indicated. This requires postulation of a potent repressant effect on growth rate as the tumor reaches the size of recognition. If growth rate is slower than calculated, then the duration of cancer is even longer than is here proposed.

Current efforts in the therapy of cancer are necessarily offered in the period of clinical observation which is here estimated to represent the final quarter of the course of the disease. Present principles of early diagnosis could extend this only to include the earliest sign or symptom which is placed at the half way mark in the development of the disease. Half the doublings necessary to kill the patient have occurred by this time. That the failures of treatment are largely due to undetected metastases present at the time of treatment is evidence that clinical diagnosis is a late event. The hope for influencing the course of cancer lies in studies of behavior in the period of undetected growth and therapeutic measures instituted close to the time of true inception of cancer.

SUMMARY

When the growth of cancer is described as a doubling process, the doubling time becomes a measure of the rate of growth. The first 20 doublings in the life of a cancer produce a minimal detectable lesion 1 mm. in diameter. The second 20 doublings increase the bulk to a kilogram of tumor tissue and bring the patient close to the termination of this disease. On the assumption of a constant growth rate, an estimate of the total duration of cancer can be made.

An estimate of the range of growth rates for a variety of human tumors was obtained from observations on pulmonary metastases as seen in serial roentgen studies. Doubling times of 11 to 164 days for growth in the period observed were encountered. If growth has progressed at this rate prior to recognition, the most rapidly growing tumor would have required seven months to reach the size of a 1 mm. nodule. The most slowly growing tumor would have required approximately nine years. Postulating a constant growth rate, the establishment of a pulmonary metastasis was earlier than the first sign or symptom of the primary lesion in all but one of the cases studied.

Some basis for assuming that the growth rate of a given tumor is the same before and after reocgnition is demonstrated by the time of recurrence of tumors in childhood. The data concerning 206 patients with Wilms' tumor were studied. A postoperative period of risk was predicted which was equal to the age of the patient at the time of diagnosis plus nine months. All recurrences fell within this period. There was no example of a patient exceeding this interval without evidence of disease who later developed recurrence. The prediction of a period of risk beyond which no recurrence will develop is a tentative, simple criterion for "cure" applicable to the individual. This goes beyond the valid statistical analysis which predicts the outcome for a group but provides no basis for individual prognosis.

A duration of cancer of the order proposed prior to detection indicates the inadequacy of current clinical concepts of early diagnosis. It also offers a plausible explanation for the late appearance of distant metastases after years of symptom free survival. A consideration of the process of growth by doubling shows that a change in growth rate is not necessary to account for the sudden appearance and seemingly rapid growth of recurrent disease.

Half the duration of development of cancer occurs before it enters the period of clinical observation. Biologic investigation and therapeutic effort must be directed to

the period of undetected growth if behavior and outcome are to be altered beyond the level of current achievement.

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EDITORIAL

ROENTGEN THERAPY

THE remarkable progress made in roentgen therapy during the past sixty years was from the beginning dependent on the constant development of increasingly powerful energizing apparatus, enabling the production of more and more penetrating roentgen rays. The range of energization during this period has been extended from the 50–100 kv. of the early primitive coils or static machines used for the activation of unprotected gas-filled tubes to the multimillion volts of present day betatrons, synchrotrons and linear accelerators.

This amazing technical achievement and gradual perfection of physical implementation have made possible the building of apparatus for almost every level of the greatly expanded range. Clinical experience has shown, however, that roentgen rays produced at four rather limited energy levels are sufficient for practical purposes. This has given rise to four forms of roentgen therapy which are known by the arbitrary names of superficial, deep, supervoltage and megavoltage roentgen therapy. For obvious reasons, the upper and lower borders of the energy levels of each of these forms is chosen likewise in an arbitrary way, especially in distinguishing megavoltage from supervoltage therapy.

Superficial roentgen therapy, which was started very soon after the discovery of the "new kind of ray" by Röntgen in 1895, is carried out with energies of 50 to 130 kv. As the name implies it is used for the treatment of superficial lesions which are located on the surface or near the surface of the body. In the early days when the roentgen rays were considered merely a variation of ultraviolet light, and no doubt as a result of the influence of the "brilliant" successes of the Finsen ultraviolet light therapy reported at the International Congress of Dermatology of Paris in 1900, they were applied much in the same manner as one would treat with ultraviolet rays. To obtain a good result with the Finsen lamp it was necessary to produce a "reaction which might vary in degree from an erythema to a vesicular or bullous dermatitis" and it was assumed that a similar reaction ought to be produced in treating with roentgen rays. This reaction was variously called "x-ray inflammation" or "x-ray burn." The lack of knowledge of the injurious effect of the roentgen rays, together with the inherent vagaries of the generating machines of that period, soon led to rather unexpected and often disastrous results, raising doubts in the minds of some authoritative investigators as to whether the use of roentgen rays for the treatment of disease should not be abandoned altogether. This uncertainty existed until the advent of the Coolidge tube in 1913, although slow improvement was made in certain technical aspects of the apparatus as well as in the use of various methods for dosage measurement. The introduction of the Coolidge tube practically revolutionized the situation. The upper range of energization was extended from the initial 100 kv. to 140 kv., more stable operating conditions were established and, because of these innovations, the clinical application was made much safer. Eventually a solid foundation was laid for the evolution of superficial roentgen therapy as we know it today.

Deep roentgen therapy had its inception in 1920, after the range of the Coolidge tube was extended to 200 kv. The greater penetration of the roentgen rays obtained at this energy level permitted adequate treatment of most deep-seated lesions and at

once gave such impetus to the clinical application of radiation that the subsequent decade must be considered as the most fertile in the entire history of the science of radiology.

This decade was also characterized by the most notable physical, biologic, physiopathologic and histopathologic contributions to the knowledge of the action of roentgen rays on normal and diseased tissues. Three very important questions came immediately to the forefront: (1) Does the action of the roentgen rays for a given exposure produce in every cell, structure or tissue an effect of the same magnitude; (2) does an identical maximal dose, whether administered singly, fractionally, or in a protracted way, produce a lethal effect on every pathologic cell, structure or tissue; and (3) if such a lethal dose is administered to any pathologic process, what reaction is there produced in the surrounding normal structures or the rest of the body?

As regards the first question, it soon became evident that each variety of cell has a specific range of sensitivity which, although influenced by extraneous factors, is a dominant feature and is related to the natural life cycle of the cell. Thus the lymphocyte with the shortest metabolic cycle is the most radiosensitive and the nerve cell with the longest life cycle is the most radioresistant. Pathologic cellular conglomerations, when structurally arranged in the simple form of a benign or malignant neoplasm, or a more complex form of heterogeneous aggregates, follow very closely the reactivity of normal cellular prototypes. These fundamental observations engendered a dosage system which, even after extension to higher energy levels, has remained unchanged in its essential features.

The second question is important from the point of view of the clinical application of the roentgen rays for therapeutic purposes and is responsible for the extremely varied methodology which has evolved during the past thirty-five years.

The third question in the beginning appeared to be of rather academic interest. As time progressed, however, it was realized that the large doses which were required to destroy especially the more resistant neoplasms, not infrequently resulted in reactions of the normal structures, leading to prolonged or permanent injury. It may be said that the decade of the 1920's was also the richest in laborious and painstaking studies of all phases of radiation-induced phenomena observed in every tissue, organ or region of the body. No thought was given then to the fact that at some future date the precise knowledge of these effects may concern the entire human race, as has happened since the world-shattering events of the atomic explosions in Hiroshima and Nagasaki.

At the present time deep roentgen therapy is carried out with 180 to 250 kv. The name "deep roentgen therapy" was originally coined to give expression to the fact that the penetration of the roentgen rays at this energy level—in contradistinction to that of superficial roentgen rays—was such that it could reach any depth of the body to be therapeutically effective. It is still the most frequently used name today although the term of medium voltage roentgen therapy, especially in comparison with supervoltage or megavoltage roentgen therapy, is occasionally employed. Because it continues to remain the most common form of radiation therapy after more than thirty-five years, it is also often referred to as conventional roentgen therapy and more recently as orthovoltage roentgen therapy.

Supervoltage roentgen therapy was introduced in the early 1930's by a few investigators using roentgen rays generated at 300 to 1,000 kv. The name of supervoltage was chosen to distinguish it from deep roentgen therapy with 180 to 250 kv. No attempt was made at that time to delimit the upper border to which the voltage could be extended. The subsequent development of the betatron in 1940, followed by the construction of other similar apparatus, soon brought to light, however, that above 5 mev. the absorption

of the roentgen rays in tissues poses, as we shall see below, new problems in clinical dosimetry. This fact makes it desirable to distinguish supervoltage therapy also from this newer type of irradiation with very high voltages for which the name megavoltage roentgen therapy has been suggested.

At the present time it is customary to designate as supervoltage therapy that form of treatment which is carried out with energies of 500 kv. to 3 mev. by using either roentgen rays or gamma rays. The former are produced by electrically operated apparatus of which the 1 mev. and 2 mev. units employing resonance transformers or electrostatic generators are the most popular. The latter are obtained from gamma-ray emitting radioactive sources housed in suitably shielded containers in large enough amounts to enable treatment at distances commonly used with roentgen rays of similar energies. Of these, radiocobalt (Co^{60}) which emits 1.17 and 1.33 mev. monochromatic rays in equal ratios and has a half-life of 5.3 years already is in widespread use and the number of new units is steadily increasing. Recently two large automatically controlled units have been installed utilizing radiocesium (Cs^{137}) which emits gamma rays of 660 kv. energy and has a half-life of 33 years. It is expected that with the completion of the Atomic Energy Commission's new fission product separation plant this isotope also will find wide use, since it offers certain advantages over radiocobalt as a teletherapy source. Radioiridium (Ir^{192}) which emits gamma rays of 800 kv. energy and has a half-life of 70 days has been successfully employed for the past six years at Addenbrooke's Hospital, Cambridge, England, mostly for short distance therapy. Other isotopes which may be considered as suitable sources for supervoltage teletherapy units are europium ($Eu^{152-154}$), tantalum (Ta^{182}) and cerium (Ce^{144}), and, of course, radium which has been used in smaller units for many years.

Supervoltage therapy, whether administered with roentgen rays or gamma rays, has three definite advantages over deep roentgen therapy. These are (1) because of the relatively greater depth dose and the lesser attenuation of the beam it permits a more homogeneous irradiation with a larger dose to a deep-seated tumor; (2) for the same reasons it allows a simplification of the technique by reducing the number of portals necessary for the purpose of cross-firing and thus reducing the extent of the reactions of the surrounding normal structures; and (3) it permits the administration of a certain physical dose to a deep-seated lesion with relatively less effect on the skin. This last advantage, which is most important from a practical standpoint is due to the fact that the maximum ionization level which at 200 kv. lies within fractions of a millimeter from the surface of the skin moves progressively below the surface as the voltage is increased, reaching a depth of about 5 mm. in the upper range of supervoltage therapy.

Megavoltage roentgen therapy is practiced with roentgen rays of multimillion volt energies, obtained from such apparatus as the betatron, linear accelerator, synchrotron, etc. The number of these apparatus has slowly increased in recent years and the range of voltage at which roentgen rays are produced by them extends from 5 to 70 megavolts. The most common are the betatrons operating at from 15 to 31 megavolts.

What makes this type of radiation distinct from the above mentioned three types is the fact that the maximum ionization lies several centimeters below the surface, and that the dose at this level may reach values several times that of the surface dose. This pattern of distribution of the radiation within the body naturally creates new problems in clinical dosimetry. Since the skin dose at the site of the incident beam represents a considerably smaller value than the depth dose, it is found more convenient, unless some biologic unit were adopted, to specify the dose at various depths by referring to the level of the maximum ionization rather than to the

surface of the skin. It is necessary to know for every voltage range applied the depth of the maximum ionization level from the skin surface, the magnitude of the dose at this level in terms of the incident physical dose, and its percentage fall-off toward the entry and, especially, the exit side of the beam.

The advantages resulting from the clinical application of megavoltage roentgen rays are being studied at the present time in several large institutions, mostly on an experimental basis. It probably will take several years before all the possibilities are fully explored and the proper therapeutic evaluations concluded. Also, it is not as yet clear which voltage range will prove most beneficial from the practical standpoint. The noteworthy advances already made in the technical methodology and physical application, however, would seem to indicate that this type of radiation, too, is gradually becoming a valuable complement of our greatly expanded treatment armamentarium.

All in all, one may say that roentgen therapy as we know it today has evolved over a period of sixty years by a process of uninterrupted accretion. Every new technical discovery, every important clinical observation, every tested principle of pathology and, not least, every fundamental medical law were utilized to build this amazingly fast developing and undoubtedly one of the most complex branches of medical science. To quote Millikan it was built "like a cathedral through the addition by many builders of many different elements."

T. Leucutia, M.D.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa. Annual meeting, Statler Hotel, Los Angeles, Calif., Sept. 25–28, 1956.

American Radium Society
Secretary, Dr. Theodore R. Miller, New York, N. Y. Annual meeting: Chateau Frontenac, Quebec, Canada, May 30–June 1, 1957.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y. Annual meeting: Palmer House, Chicago, Ill., Dec. 2–7, 1956.

American College of Radiology
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: 1957, to be announced.

Section on Radiology, American Medical Association
Secretary, Dr. T. Leucutia, Harper Hospital, Detroit 1, Mich. Annual Meeting, June 3–7, 1957, New York, N. Y.

Eighth International Congress of Radiology
Secretary General, Dr. José Noriega, Calle del Oro 15, Mexico 7, D. F.

Alabama Radiological Society
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

American Nuclear Society
Dr. L. D. P. King, Los Alamos Scientific Laboratory, Post Office Box 1663, Los Alamos, N.M. Winter meeting, Sheraton-Park Hotel, Washington, D.C., Dec. 10–12, 1956.

Arizona Radiological Society
Secretary, Dr. J. J. Riordan, 550 W. Thomas Rd., Phoenix, Ariz. Two regular meetings a year. The annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Dr. E. A. Mendelsohn, Holt-Krock Clinic, Fort Smith, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary, Dr. David M. Gould, University of Arkansas Medical Center, Little Rock, Ark. Annual meeting, May, 1957 at the University of Minnesota.

Atlanta Radiological Society
Secretary, Dr. Charles M. Silverstein, 3254 Peachtree St., N.E., Atlanta, Ga. Meets monthly, except during three summer months, on second Friday evening.

Blockly Radiological Society
Secretary, Dr. Samuel Finkelman. Annual dinner: May, 1956.

Brooklyn Radiological Society
Secretary, Dr. Theodore Kamholtz, 152 Clinton Street, Brooklyn, N. Y. Meets first Thursday of each month October through May.

Brooklyn Roentgen Ray Society
Secretary, Dr. J. J. Daversa, 345 75th St., Brooklyn, N.Y. Meets monthly fourth Tuesday, October through April.

Buffalo Radiological Society
Secretary, Dr. Charles Bernstein, 685 Delaware Ave., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Roentgen Ray Society
Secretary, Dr. Dwig ht V. Needham, 608 E. Genesee St., Syracuse, N. Y. Meets January, May, November.

Central Ohio Radiological Society
Secretary, Dr. Arthur R. Cohen, 41 S. Grant Ave., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary, Dr. Arthur S. J. Petersen, 11406 Parnell Ave., Chicago 28, Ill. Meets second Thursday of each month, October to April inclusive at the Sheraton Hotel.

Cleveland Radiological Society
Secretary, Dr. A. S. Tucker, 2065 Adelbert Rd., Cleve land 6, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

Colorado Radiological Society
Secretary, Dr. Dorr H. Burns, 1776 Vine St., Denver, Colo. Meets third Friday of each month at University of Colorado Medical Center or at Denver Athletic Club.

Connecticut Valley Radiologic Society
Secretary, Dr. T. J. Crowe, 53 Center St., Northampton, Mass. Meets second Friday October and April.

Dallas-Fort Worth Radiological Club
Secretary, Dr. A. H. Keene, 3707 Gaston Ave., Dallas, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Joseph O. Reed, Jr., Harper Hospital, Detroit, Mich. Meets monthly first Thursday, Oct. through May, at David Whitney House, 4421 Woodward Ave., at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

Florida Radiological Society
Secretary, Dr. C. Robert DeArmas 135 Broadway, Daytona Beach, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

Georgia Radiological Society
Secretary, Dr. B. H. Malone, 1406 Reynolds St., Brunswick, Ga.

Greater Miami Radiological Society
Secretary, Dr. A. S. Capi, 300 N. 20th Ave., Hollywood, Fla. Meets monthly third Wednesday at 8 P.M. at Mercy Hospital, Miami, Fla.

Greater St. Louis Radiological Society
Secretary, Dr. Sam J. Merenda.

Houston Radiological Society
Secretary, Dr. Leslie L. Lemak, 616 Medical Arts Bldg., Houston 2, Texas. Meets fourth Monday each month, Meeting Room, Doctors' Club of Houston.

Idaho State Radiological Society
Secretary, Dr. Alfred M. Stone. St. Lukes Hospital, Boise, Idaho. Meets annually at same time as Idaho State Medical Association.

Illinois Radiological Society
Secretary, Dr. Stephen L. Casper, 1101 Maine St., Quincy, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. C. A. Stayton, 313 Hume-Mansur Bldg., Indianapolis 4. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

* Secretaries of societies are requested to send timely information promptly to the Editor.

Iowa Radiological Society
Secretary, Dr. James T. McMillan, 1104 Bankers Trust Bldg., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary, Dr. A. M. Cherner, Hays, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. David Shapiro, 217 East Chestnut St., Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Solomon Maranov, 1450 51st St., Brooklyn 19, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Lewis J. Peha, 405 North Bedford Drive, Beverly Hills, Calif. Meets second Wednesday each month at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. Irving L. Selvago, Jr., Maine Medical Center, 22 Arsenal St., Portland, Maine. Meets in June, September, December and March.

Maryland Radiological Society
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore, Md.

Memphis Roentgen Society
Secretary, Dr. Dan C. Gary, 36 South Bellevue, Memphis 4, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. G. A. Nicoll, 134 Apple St., Dayton, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. J. W. Walton, Horton Memorial Hospital, Middletown, N. Y. Meets 8:30 P.M., fourth Tuesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. R. W. Bryne, 3321 N. Maryland Ave., Milwaukee 1, Wis. Meets monthly on fourth Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. O. J. Baggenstoss, 1953 Medical Arts Bldg., Minneapolis, Minn. Meets three times annually, once at time of State Med. Assn., and in spring and fall.

Mississippi Radiological Society
Secretary, Dr. James M. Packer, 621 High St., Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
Secretary, Dr. John Stewart, 1105 Frederick Lane, Billings, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Frances Behrendt, 19 Clinton Rd., Garden City, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. J. F. Kelly, Jr., 816 Medical Arts Bldg., Omaha, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Raymond A. Dillon, 24 Wedgemere Ave., Winchester, Mass. Meets third Friday of each month, October through May, at Hotel Commander, Cambridge, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. John A. Evans, 525 East 68th St., New York 21, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. William H. Sprunt, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. Marianne Wallis, St. Joseph's Hospital, Minot, N. D. Meetings by announcement.

North Florida Radiological Society
Secretary, Dr. Marvin Harlan Johnston, Five Points Medical Center, Jacksonville, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Irving Van Woert, Jr., Albany Hospital, Albany, N. Y. Meets in Albany area on second Wednesdays of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. H. B. Stewart, 2920 Capital Ave., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. John R. Hannan, 10515 Carnegie Ave., Cleveland 6, Ohio. Annual meeting, Dayton, May, 1957, to be announced.

Oklahoma State Radiological Society
Secretary, Dr. Sol Wilner, St. John's Hospital, Tulsa, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. N. L. Bline, 210 Jackson Tower, Portland 5, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. J. R. Raines, 214 Medical-Dental Bldg., Portland 5, Oregon. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Walter P. Bitner, 234 State Street, Harrisburg, Pa.

Philadelphia Roentgen Ray Society
Secretary, Dr. Roderick L. Tondreau, 3400 Spruce St., Philadelphia, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. N. B. Tannehill, 601 Jenkins Bldg., Pittsburgh 22, Pa. Meets second Wednesday of month, October through June at Hotel Roosevelt.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Paul W. Roman, 1810 Eutaw Place, Baltimore 17, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of Greater Cincinnati
Secretary, Dr. R. J. Neubauer, 831 Carew Tower, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. Richard D. Moore, St. Francis Hospital, Honolulu 17, T. H. Meets third Monday evening of each month at designated hospitals.

Radiological Society of Greater Kansas City
Secretary, Dr. E. H. Stratemeier, Jr., 1010 Rialto Building, Kansas City 6, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. W. S. Neal, 602 Pere Marquette Bldg., New Orleans, La. Meets annually during Louisiana State Medical Society Meeting.

Radiological Society of New Jersey
Secretary, Dr. G. G. Green, 601 Grand Ave., Asbury Park, N. J. Meets at Atlantic City at time of State Medical Society and in November in Newark, N. J.

Radiological Society of Southern California
Secretary, Dr. Robert B. Engle, 2632 E. Washington St., Pasadena, Calif.

Richmond County Radiological Society
Secretary Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Henry H. Forsyth, Jr., 40 Meigs St., Rochester, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth St., Denver 20, Colo.

St. Louis Society of Radiologists
Secretary, Dr. Edwin C. Ernst, Jr., 3720 Washington Ave., St. Louis 8, Mo. Meets fourth Wednesday each month, except June, July, Aug. and Sept.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets Brooke Army Medical Center Officers Mess second Wednesday of each month.

San Diego Radiological Society
Secretary, Dr. J. C. Asher, 2001 Fourth Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Howard L. Steinbach, University of California Medical Center, San Francisco 22, Calif. Meets quarterly at Grison's Steak House.

Section on Radiology, California Medical Association
Secretary, Dr. A. R. Wilson, 540 North Central Ave., Glendale 3, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. J. Burbank, Meriden Hospital, Meriden, Conn. Meetings are held bi-monthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. Melvin O. Goodman, 1930 K St., N.W., Washington 6, D. C. Meets Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. George E. Irwin, Jr., 703 N. East St., Bloomington, Ill.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M. September to May inclusive.

Society of Nuclear Medicine
Secretary, Dr. Robert G. Moffat, B. C. Cancer Institute, 2656 Heather Street, Vancouver 9, Canada. Annual meeting, to be announced.

South Bay Radiological Society
Secretary, Dr. T. N. Foster, 630 E. Santa Clara St., San Jose, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. S. W. Lippincott, 103 Rutledge Ave., Charleston, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

Southwestern Radiological Society
Secretary, Dr. Gordon Black, Suite 2-A, El Paso Medical Center, 1501 Arizona, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
Secretary, Dr. G. K. Henshall, 311 Medical Arts Bldg., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. J. E. Miller, Baylor Hospital, Dallas, Texas. Next meeting, Corpus Christi, Texas, Jan. 18–19, 1957.

Tri-State Radiological Society
Secretary, Dr. Robert E. Beck, 600 Mary St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May, Service Memorial Institute.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Eva L. Gilbertson, 1317 Marion St., Seattle 4, Wash. Meets fourth Monday of each month from September through May at 610 Pine St., Seattle.

West Virginia Radiological Society
Secretary, Dr. W. Paul Elkin, 515 Medical Arts Bldg., Charleston, W. Va. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. M. G. Priestman, New Rochelle Hospital, New Rochelle, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. W. W. Moir, 309 Geele Ave., Sheboygan, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-Ray Study Club of San Francisco
Secretary, Dr. J. T. English, 2000 Van Ness Ave., San Francisco 9, Calif. Meets monthly, third Thursday at 7:45 P.M., Lane Hall, Stanford University Hospital.

Cuba, Mexico, Puerto Rico and Central America

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San Jose, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15, Mexico 7, D. F.
Secretary General, Dr. Guillermo Santín. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Diaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sanchez, Apartado No. 86, Panama, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Empire

Association of Radiologists of the Province of Quebec
Secretary, Dr. Isadore Sedlezky, 3755 Cote St. Catherine Rd., Montreal, Que. Meets four times a year.

British Institute of Radiology Incorporated with the Röntgen Society
Ordinary meeting, on the Thursday preceding the third Friday, October to May at 8:15 P.M.
Medical Members' meeting, on third Friday in each month at 5:00 P.M., 32 Welbeck St., London, W 1

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 45, Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary-Treasurer, Dr. Guillaume Gill, Suite 305, 1555 Summerhill Avenue, Montreal 25, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicales
General Secretary, Dr. Ls Ivan Vallée, 1058 rue St-Denis, Montreal 18, Canada. Meets third Saturday each month.

College of Radiologists (Australia and New Zealand)
Honorary Secretary, Dr. Alan R. Colwell, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W.

South America

Asociacion Argentina de Radiologia
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151 Córdoba, Argentina. Meetings held monthly.

Sociedad Argentina de Radiologia, Junta Central, Buenos Aires
Secretary, Dr. Oscar F. Noguera, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Argentina de Radiologia, Filial del Litoral, Sede, Rosario
President, Dr. Francisco P. Cifarelli. Meets monthly second Wednesday, 19 ha 663 Italia St., Rosario, Santa Fe.

Sociedad Argentina de Radiologia, Filial del Sur, Sede, La Plata
President, Prof. Dr. Jose P. Uslenghi, La Plata. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Centro Sede, Córdoba
President, Prof. Dr. David L. Caro, Corro 86, Córdoba. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Norte, Sede, Tucuman
President, Dr. Julio Mendez Valladares, Rivadavia 358, Tucuman. Meets monthly.

Sociedad Argentina de Radiologia, Filial de Cuyo Sede, Mendoza.
President, Dr. J. A. Orfila, Hospital Central, Mendoza. Meets monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Colombiana de Radiologia
Secretary, Dr. Luis E. Lozano B., Carrera 12 No. 20–69, 6° piso, Bogota, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiologia y Fisioterapia
Secretary, Dr. Enrique Ortega Guzmán, Casilla 4719, Guayaquil, Ecuador.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos G. Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary General, Dr. Roberto Francois, Av. Agraciada 1464, Piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad Venezolana de Radiología
Secretary, Dr. Otto Paz, Centro Médico, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Austrian Roentgen Society
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Société Française d'Electro-Radiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord
Secretary-General, Dr. A. Dariaux, 9 bis, Boulevard Rochechouart, Paris IX°, France.

Ceskoslovensk společnost pro rëntgenologii a Radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgen-Gesellschaft
Secretary, Dr. med. Peter Kröker, Evangelisches Krankenhaus, Huyssens Stiftung, (22a) Essen.

Societa Italiana di Radiologia Medica
Secretary, Prof. Mario Ponzio, Ospedale Mauriziano, Torino, Italy. Meets biannually.

Nederlandse Vereniging voor Electrologie en Roentgenologie
Secretary, Dr. B. J. Rethmeier, Bornsestraat 378, Almelo, Netherlands.

Polish Society of Radiology
Secretary, Dr. Juljusz Borejko, 59 Nowogrodzka St., Warsaw, Poland.

Gdansk Section, Polish Society of Radiology
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10:30, X-Ray Dept., Akademia Gdansk.

Wroclaw Section, Polish Society of Radiology
Secretary, Dr. R. Marciniak, Akad. Medyczna Wroclaw, 68 Curie-Sklodowska St., Wroclaw, Poland. Meets first Sunday of each month, X-Ray Department, Akademia Medyczna Wroclaw.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S.I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad
USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiologia y Electrologia
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgen-Gesellschaft (Société-Suisse de Radiologie)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The list of Meetings of Radiological Societies is published in every other issue of the Journal.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

A. Liechti—Röntgenphysik. Dr. Phil. Walter Minder, Dozent für Physikalische Grundlagen der Medizinischen Radiologie, Leiter des Radium-Institutes Bern. Second edition. Cloth. Price $12.85. Pp. 306, with 264 illustrations. Springer-Verlag, Mölkerbastei 5, Wien, Austria, 1955.

The first edition of this popular book was published in 1939 by Adolph Liechti, M.D., Professor of Medical Radiology at the University of Bern, Switzerland. It contained contributions by Walter Minder, Ph.D., on "Production of Radioactive Radiation," "The Measurement of Radium Rays (α, β and γ rays)," and "Non-Medical Uses of Roentgen Rays." The book was very well received by the profession and was among the publications which, during the second world war, were lithoprinted in the United States by authority of the Alien Property Custodian and sold in Europe after the war.

After the death of Dr. Liechti, his former collaborator began a thorough revision of the text and now offers the second edition of "Röntgenphysik." In his foreword the author states that the book is primarily written for the radiologist, but is also intended for the radiation physicist and radiation biologist. Consequently the scope of the material goes somewhat beyond the contents of most American textbooks on radiologic physics. Practical and theoretical physics are emphasized to a larger extent than in the first edition. The fundamental chapters on the character and properties of roentgen rays, structure of matter, absorption and scattering, roentgen-ray generators and roentgen-ray tubes are well written and illustrated, although the material is routine. Some of the technical constructions are described in great detail to an extent that may go beyond the actual interest of the radiologist. One could mention here the description of the gas tube, variety of focal spots, details of high voltage cables, induction coils, hand operated and mechanical switches. The van de Graaff electrostatic generator, resonance transformer, linear accelerator, betatron and synchrotron are briefly described.

The second section of the book deals with the physical effects of roentgen rays (photoelectric effect, luminescence, color changes, Cerenkow radiation, ionization, heat production), the chemical effects of these rays (on colloids, disperse molecular systems, photographic emulsion), and the biological effects, together with several theories on the production of such effects. Measurements of radiation quality by means of the spectrometer, sphere gaps, and filter analysis (absorption curve, half-value layer and effective wave length) are described in great detail. Equally thorough is the presentation of radiation quantity measurements and instrumentation. Measurement of ionization in pure air and in air-equivalent material is explained. Historical and modern units of radiation (except the "rad") are presented. A detailed list of the many dosimeters used in Europe (Küstner barrel chamber, Hammer dosimeter, Mekapion, Siemens universal dosimeter, ionognom), most of them equipped with a variety of ionization chambers, such as the grenz-ray chamber, pot-chamber, high-intensity chamber, contact-therapy chamber, and scattered radiation chamber, is given. This chapter also contains a few pages on tissue dosages on the surface and in the depth for various radiation qualities and their dependence upon focal distance, size of field, and quality. Increasing the depth dose by the use of moving-beam radiation and the use of a grid is explained. Measures for radiation protection are rather briefly described and the use of pocket dosimeters or film badges is recommended.

The book ends with a chapter on "Auxiliary Apparatus, Auxiliary Methods in Medical Roentgenology," and describes the optics of the roentgen-ray picture, geometric projections, position of object, source of radiation and recording material, radiation diaphragms, kymography and cinematography, laminagraphy, stereography and cineradiography. In an addendum, nonmedical uses of the roentgen rays are given. They include examination of paintings with roentgen rays, gross- and fine-structure examination, and spectral analysis of matter in crystal or powder form.

The book is well written and illustrated. The

179 line-drawing illustrations are especially good, while a number of the half-tones, by their very nature do not seem to present a good picture of the apparatus involved. The book, although more technical than its American counterparts, can be highly recommended.

Otto Glasser, Ph.D

The Microstructure of Starch Grains. By Edith A. Roberts. Paper. Author's address: 17 Dearborn Street, Salem, Massachusetts, 1956.

The introduction of this monograph is concerned with an excellent historical background of the theories and work done on the structure of starch up to the present time. Many references are cited.

The primary objective is to report experimental work on the microphysical structure of starch grains and plastids. The results satisfy and explain previous controversial investigations and lay the theoretical foundation for future research and applications to industrial and home economic problems.

Over 100 photomicrographs are reproduced to illustrate the importance of past research to the present investigation, as well as those taken during study of the present problem. In this recent work high voltage roentgen therapy and the ultraviolet microscope were the newer tools used, along with well established procedures.

Roberts shows quite conclusively that the grain structure of starch is the same, basically, as plastids in leaves and stems. The fundamental microphysical structure of the starch grain is that of a network or "protoplasmic framework" in which the starch is formed. Microphotographs are reproduced showing the various changes in starch due to roentgen rays, and even the destruction of the starch with little or no effect on the framework. These experiments were carried out under varying conditions of temperature and moisture with different voltages.

The differential effect of the high voltage roentgen rays on the starch structure has been determined by means of the ultraviolet and the standard microscopes.

This work is an excellent example of the use of one of the newer tools, therapeutic high voltage roentgen rays, to the study of growth and cell structure which is so basic to most of the research problems of today.

Henrietta S. Hayden, Ph.D.

Breast Cancer and Its Diagnosis and Treatment. By Edward F. Lewison, B.S., M.D., F.A.C.S., Assistant Professor of Surgery, Johns Hopkins University School of Medicine; Surgeon, Johns Hopkins Hospital; Surgeon, Out-Patient Department, Breast Clinic, Division of Tumor Clinic, Johns Hopkins Hospital. Cloth. Price, $15.00. Pp. 478, with 181 illustrations. Williams & Wilkins Co., Mt. Royal and Guilford Avenues, Baltimore 2, Maryland, 1955.

In the words of the author, the purpose of this book has been to sift the vast store of available information concerning breast cancer, combine it with practical precepts of clinical experience and make it available to all interested in the total care of the disease. In this, the first comprehensive American book devoted to mammary cancer to be written in more than a quarter of a century, the author achieves his objective by examination of virtually every significant aspect of the disease.

Seven of the twenty chapters were contributed by collaborators of distinction in their respective fields. A particularly interesting section on the history of the disease and its treatment is followed by chapters on surgical anatomy, physiology, pathology, diagnosis, biopsy, surgical treatment, radiotherapy, hormonal therapy, prognosis and statistics.

A lucid style with frequent felicitous phraseology and pointed quotations, coupled with excellent illustrations, make this book a pleasure to read. The author remains a protagonist of the radical mastectomy. Although crediting McWhirter with having achieved comparable five-year survival rates, it is the author's opinion that the thesis, simple mastectomy plus irradiation as the treatment of choice, is not proved.

This text is a valuable addition to the literature on cancer of the breast, particularly for those faced with the practical problems of treating this most common female cancer.

Isadore Lampe, M.D.

Small-Angle Scattering of X-Rays. André Guinier, Professor, Université de Paris (France), and Gérard Fournet, Lecturer, École Supérieure de Physique et Chimie, Paris. Translation by Christopher B. Walker, Institute for the Study of Metals, University of Chicago. Paper. Price, $7.50. Pp. 268, with 78 illustrations. John Wiley & Sons, Inc.

440 Fourth Avenue, New York 16, New York, 1955.

The authors faced a major task in trying to organize this material and put it in the form of a single book. They have done an excellent job. This volume can serve as a basic manual of real value to the beginner in the field or as a reference for the advanced worker. The introductory chapter on the origin and characteristics of small-angle scattering occupies only four pages but outlines the subject effectively.

Chapter II on general theory is excellent from the point of view of presenting all of the fundamentals, and it is sufficiently complete to satisfy anyone but an advanced worker dealing with certain highly specialized aspects. The authors actually have done well to avoid getting into some of the ancillary material.

The chapter on experimental equipment may leave something to be desired, but since this subject would require more than the entire volume for complete coverage, again, it can be said that the authors have shown good judgment. All of the fundamental concepts are discussed.

The chapters on interpretation of results and application are again more in the nature of reference material, giving brief descriptions of the application of both theory and procedure to the study of specific problems. There are sections on such subjects as high polymers and fiber structures, and orderly arrangement of micelles that have direct application to the study of many structures which are fundamentally important in the life sciences, including medicine.

Chapter V, entitled "Comparison of the Results from Small-Angle Scattering with the Results of Other Methods of Measurement of Small Particles," comprises only six pages to set forth the relationships between the small-angle technique and the electron microscope or the Debye-Scherrer diffraction measurements. These six pages, however, offer a far better comparison than is to be found in some descriptions of much greater length. There is an excellent bibliography, and the whole book is organized from the point of view of easy study and good practical application.

This book should be in the library of every teaching and research institution and will be of real value to those interested in the borderline along which science must advance.

Henrietta S. Hayden, Ph.D.

Nuclear Radiation Detectors. By J. Sharpe, B.Sc., A.M.I.E.E., Late of Atomic Energy Research Establishment, Harwell. Paper. Price, $2.50. Pp. 184, with tables and illustrations. John Wiley & Sons, Inc., 440 Fourth Avenue, New York 16, New York, 1955.

This book is well organized and covers all of the general classes of counters in excellent detail. It is neither a textbook nor a laboratory manual but it occupies a place between the two.

Although he does not give construction details of counters, the author explains where these are to be found for their particular classes. The volume includes the theory of each type of counter, from the most basic concepts to a rather well developed level. Thus, the reader is given a clear view of how and why each type works.

This will be a useful book to anyone having a basic knowledge of the subject but wanting a well condensed reference for teaching, or to confirm for himself details of the fundamental theory, particularly of counters and ionization instruments other than those with which he is thoroughly acquainted.

K. E. Corrigan, Ph.D.

Trabajos de Oncología y Radioterapia, Años 1953–1954. Publicaciones del Instituto de Radiología y Ciencias Físicas Bajo la Dirección del Prof. Alfonso C. Frangella, Director Interino del Instituto, Prof. Honorario F. de Medicina Universidad Nal. de Colombia. Paper. Pp. 525, with tables and illustrations. "Rosgal," Montevideo, Uruguay, 1955.

Professor Frangella has collected in this volume a series of papers which were presented at the Institute of Radiology by members of his staff and by distinguished visitors during 1953–1954.

There are several excellent papers on leukemia, which is studied from a statistical, clinical, cytologic, histopathologic and therapeutic point of view. There is a very thorough presentation of malignant melanoma by Professor C. A. Pantoja of Bogotá and a very commendable discussion of the methods of treatment of cancer of the nasopharynx by Dr. H. Kasdorf. Numerous other papers contribute to making this volume a worthy possession.

J. A. del Regato, M.D.

Autoradiography in Biology and Medicine. By George A. Boyd, Director, Arizona Research Laboratories, Phoenix, Arizona. Formerly, Professor of Biophysics, University of Tennessee, and Senior Scientist, Oak Ridge Institute of Nuclear Studies. Cloth. Price, $8.80. Pp. 399, with 98 illustrations. Academic Press Inc., Publishers, 125 East 23 Street, New York 10, New York, 1955.

The book is primarily a compilation of all of the autoradiographic techniques that have proved to be practical and valuable. The interesting historical introduction is followed by a section on the theory of the photographic process. There is also a section on available commercial photographic materials, as well as a theoretical discussion which lays the basis for all of the practical procedures. These chapters include numerous tables of useful information.

The second part of the book has to do entirely with techniques and is divided, insofar as possible, according to the type of specimen to be studied and the methods applicable to each specimen. The author has gone to a great deal of trouble to find and present the best methods and to bring out the most straightforward and practical techniques. One of the particularly helpful chapters is on sources of error. The author goes into considerable detail about those processes which will either cause loss of the true image or produce a false image. This is a section with which any one attempting this type of work should be thoroughly familiar.

The book ends with a 50-page bibliography which is further supplemented by references through 1953. There is a classified subject index and an author index.

The book could only be written by a person who has complete mastery of the procedures described. The author has collected and presented the work of the most authoritative investigators in many fields.

K. E. Corrigan, Ph.D.

Causal Factors in Cancer of the Lung. By Carl V. Weller, M.S., M.D., Chairman of the Department of Pathology and Professor of Pathology in the Medical School, and Pathologist to the University Hospital, University of Michigan, Ann Arbor, Michigan. Cloth. Price, $3.00. Pp. 113, with 20 illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1956.

This monograph is essentially the Beaumont Lecture for 1955 given before the Wayne County (Michigan) Medical Society by the author and is one of the American Lecture Series of monographs. Written by a pathologist of long experience and international reputation, it is a concise review and analysis of lung cancer in relation to occupations and in relation to cigarette smoking.

It is not entirely correct to say that the causes of lung cancer are unknown. Dr. Weller points out that an increased incidence of bronchogenic carcinoma has been demonstrated in workers exposed to chromates, arsenic, asbestos, nickel refining, processing of certain metals, and certain tars in the production and distribution of gas. In addition, it has been known for hundreds of years that the miners in certain areas of Saxony and Bavaria have had a high incidence of a lung disease, now known to be cancer, probably due to exposure to radioactive dust or arsenic.

The author discusses the evidence relating lung cancer and smoking. Several different statistical methods of assay show an association between heavy cigarette smoking and lung cancer. Although the association is not necessarily causal, no other explanation is presently available.

Dr. Weller mentions "intrinsic" causes of lung cancer (those in the germ plasm), but the only one known that may have validity is "maleness." He believes that sequential, synergistic and additive effects need more attention.

As a condensed review of the subject, as a source for some statistical material, and particularly as a survey of occupational induction of lung cancer, this volume is well worth the short time it takes to read it.

Henry J. Klos, M.D.

Symposium on Genetic Recombination. Sponsored by The Biology Division, Oak Ridge National Laboratory. Paper. Free of charge to scientific investigators. Pp. 321, with 46 illustrations. Oak Ridge National Laboratory, Post Office Box Y, Oak Ridge, Tennessee, 1955.

This book consists of 16 chapters on lectures given by 19 authors at a Research Conference for Biology and Medicine of the Atomic Energy Commission at Oak Ridge, Tennessee, in April, 1954. Most chapters deal with highly specialized work in bacterial genetics, transformation and transduction, methods which

have furnished new approaches to the genetic study of higher organisms. Reports on these studies, on recombination theory and mechanism, crossovers, and on the oxygen effect on radiation-induced chromosome aberrations are presented. Occasionally the new approaches to genetic studies do not seem to be in accord with the classical methods, a fact brought out in a poem written by R. D. Hotchkiss, one of the speakers, and presented as the concluding remarks on the Symposium on Genetic Recombination. The last verse of this poem reads:

> Now, lest we be too placid—
> There might be other genes
> That instead of nucleic acid
> Are made up of proteins.
> How perverse our limitations—how incredibly tragic
> That, for each and every one of us, one or the other of these two hypotheses should seem relatively acceptable and the alternative one should seem like believing in magic.

Otto Glasser, Ph.D.

Biological Hazards of Atomic Energy; Being the Papers Read at the Conference Convened by the Institute of Biology and Atomic Scientists' Association, October, 1950. Edited by A. Haddow. Cloth. Price, $8.00. Pp. 235, with numerous illustrations. Oxford University Press, 114 Fifth Avenue, New York 11, New York, 1953.

This volume contains 24 papers representing the proceedings of the Conference on the Biological Hazards of Atomic Energy held at the Royal Institution in October, 1950. The Conference was sponsored by the Institute of Biology and the Atomic Scientists' Association, with the support of the British Association and the British Institute of Radiology.

The purpose of the Conference was to discuss the biological hazards associated with the development and application of atomic energy, both now and in the future. In each paper, a well-known expert discusses some aspect of a general subject on which he is an authority. Comprehensive surveys are made of what is already known in the field and in many instances the direction for future investigation is suggested.

General papers are devoted to the genetic effects of ionizing radiation. This aspect of radiobiology is covered rather completely, and there is an explanation of the mechanisms by which ionizing radiations affect chromosomes and genes. These discussions outline the experimental results and conclusions of some of the outstanding workers in this field. Other aspects of radiobiology treated include the effects of radiation on living cells, the effects of different types of ionizing radiation, and the carcinogenic effects of ionizing radiation.

Another series of papers deals with radiological protection, both of radiological workers and the general population. These papers emphasize the basis for establishing radiation tolerance levels and review the history of the organization of radiation protection, committees, control of radiation hazards at AERE, Harwell, and radiation exposures in Sweden.

A review is made of precautions, simple equipment and protective techniques for a clinical radioiodine program. Considerations governing the use of radioactive iron in humans are discussed from the standpoint of dosimetry and criteria for safe dosage.

An interesting paper is presented on the biological hazards of radioactive strontium. This paper emphasizes some of the more significant aspects of the physiological behavior of strontium 90 and yttrium 90 and ways of removing these isotopes from the bone.

Two papers deal with the chemical and physiological basis of protection from ionizing radiation and summarize some of the experimental results up to the date of the conference.

The remainder of the papers cover such subjects as the retention of carbon-14 by adult and embryonic mice, the measurement of radioactivity in the human body by high pressure ionization chambers, and the moral issue of atomic energy.

As in the published papers of most conferences such as this, there is some repetition. Also, some of the papers are necessarily brief and do not provide as much information on a particular subject as one might desire, but they are, in general, well presented. Furthermore, the papers are written so that a person with even a limited background in biology will find them readable and informative.

This volume makes a worthwhile contribution to the field of radiobiology.

G. W. Morgan, M.A.

Handbook of Radiology. Edited by Russell H. Morgan, M.D., Professor of Radiology,

School of Medicine, The Johns Hopkins University, Radiologist-in-Chief, The Johns Hopkins Hospital; Associate Editor, Kenneth E. Corrigan, Ph.D., Associate Professor of Radiology, Wayne University; Director, Radiological Research Department, Harper Hospital, Detroit. Cloth. Price, $10.00. Pp. 518, with numerous illustrations. The Year Book Publishers, Inc., 200 East Illinois Street, Chicago 11, Illinois, 1955.

The compiler of an anthology or a volume of collected data cannot hope to satisfy all his readers; however careful the selection, there will always be omissions which to some obviously should replace material included. For this reason, any review must necessarily reflect the outlook of the reviewer.

This handbook, the work of 15 collaborators, is designed to collect data, mainly of a quantitative nature, covering the field of radiology in its clinical, experimental and industrial applications and it appears to have been admirably successful. The text is divided into six main sections: Definitions of Physical Terms and Units; General Physical Information, which includes mass and atomic absorption coefficients and initial energy distributions and ranges of electrons in water; Radiotherapeutic Data and the following section on Radioisotopes, which together provide a comprehensive collection of depth dose information and methods of dosimetry, particularly as related to biology and medicine; Radiography and Fluoroscopy, a survey of the characteristics of medical and industrial materials and apparatus, comprising data on accepted contrast media and standard radiographic techniques; Radiation Protection, a discussion in terms of roentgen rays, radium and radioisotopes. Four appendices cover common drugs, mathematical tables, the Greek alphabet and schematic diagrams of generators and accelerators.

The small page size, while ideal for a handy reference book, is not adapted to the graphical presentation of data and, wisely, these are given mainly as tables. Where graphs have been used, they are clear and legible. In general, sources of information and references to original material are well documented.

It might be questioned whether the scope of this work has not been too inclusive. The physicist or radiation therapist referring frequently to the first four sections may rarely, if ever, have occasion to employ the data on radiography, while the diagnostician will make equally little use of some of the earlier material. There would appear to be advantages, and possibly many complications, which have no doubt, already been considered by the editors, in a two-volume edition.

The production of a publication of this type entirely free from errors in its first edition would be a considerable achievement, but those which have been noted are mainly of a minor nature. The roentgen-ray depth dose tables are for open ended ports only and in terms of air dose, but it is surely more in accord with modern practice to use closed ended ports and surface dose. Tables in this form, either instead of, or in addition to, those given, would have been very helpful. In the radium data Sievert's formula for linear sources is given, but an extract from the original tables adapted to common filtrations would have been especially valuable.

Raymond S. Quick

BOOKS RECEIVED

Cancer of the Lung; An Evaluation of the Problem. Proceedings of the Scientific Session, Annual Meeting, American Cancer Society, Inc., November 3–4, 1953. Paper. Pp. 322, with illustrations. The American Cancer Society, Inc., 521 West 57th Street, New York 19, New York, 1956.

Roentgen Signs in Clinical Diagnosis. By Isadore Meschan, M.A., M.D., Professor and Director of the Department of Radiology at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina; with the assistance of R. M. Farrer-Meschan, M.B., B.S., (Melbourne, Australia). Cloth. Price. $20.00. Pp. 1058, with 2,216 illustrations on 780 figures. W. B. Saunders Company, West Washington Square, Philadelphia 5, Pennsylvania, 1956.

Dermatology. By Donald M. Pillsbury, M.A., D.Sc. (Hon.), M.D., Professor and Director of Department of Dermatology, University of Pennsylvania School of Medicine; Walter B. Shelley, M.D., Ph.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine; and Albert M. Kligman, M.D., Ph.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine. Cloth. Price, $20.00. Pp. 1,331, with 564 figures. W. B. Saunders Company, West Washington Square, Philadelphia 5, Pennsylvania, 1956.

The Microstructure of Starch Grains. By Edith A. Roberts. Paper. Author's address: 17 Dearborn Street, Salem, Massachusetts, 1956.

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Head

Tänzer, A. Die basiläre Impression. (Basilar impression.) *Radiol. clin.*, March, 1956, *25*, 135–152. (Address: Röntgeninstitut und Strahlenklinik der Städtischen Krankenanstalten, Beurhausstrasse 40, Dortmund, Germany.)

Basilar impression, defined as a cephalad projection of the foramen magnum region, has been variously referred to as basilar invagination, plastic deformity of the base of the skull, aplatissement of the cranial base, and platybasia (the latter term being considered incorrect and referring to another entity). In mild cases only the occipital condyles are displaced upwards; in more advanced cases, the clivus participates; in severe instances, the entire region of the foramen magnum is involved. In primary (or congenital) basilar impression, the changes are due to an anomaly and the osseous architecture is normal roentgenographically. In secondary (or acquired) basilar impression, osteoporotic conditions (such as rickets, osteomalacia, senile atrophy, and Paget's disease) are the underlying features; craniocleidodysostosis is a frequent causative factor in basilar impressions of the acquired type.

Embryologically, the atlanto-occipital region is subject to dynamic forces which tend to cause a caudad shift of the craniovertebral boundary. The so-called vertebral area of the occiput is derived from the fusion of four vertebral centers. The body of the pro-atlas forms the tip of the odontoid process and the arch of the pro-atlas forms the bridge over the sulcus for the vertebral artery. The canal for the hypoglossal nerve corresponds to an intervertebral foramen. Knowledge of embryologic data will help to avoid errors in diagnosis, especially in conditions of hypoplasia of the occipital condyles or atlas and in assimilation of the atlas.

To aid in the diagnosis of basilar impression, several measurements of the skull have been described by Boogard, Chamberlain, McGregor, and others. Measurements, which include the margins of the foramen magnum, are not always useful, especially on conventional films because it is frequently difficult to identify these landmarks. Furthermore they refer only to relationships of mid-line structures, so that they only indirectly reflect the position of paramedian sites, such as the occipital condyles. While the author makes use of the various well-known measurements of the basal angle, Chamberlain's line and McGregor's line, he advises the use of laminagraphy to determine two other measurements introduced by Fischgold and Metzger. The bimastoid line joins the tip of the mastoid process on each side, passes through the atlanto-occipital joint, and normally lies 1 to 2 mm. below the tip of the odontoid process. The digastric line is drawn from a point which marks the transition from the mastoid process to the floor of the posterior fossa across to the same point on the opposite side. The latter line is especially important since it relates directly to the floor of the posterior fossa; it is about 1 cm. above the bimastoid line. The floor of the posterior fossa is above the digastric line in basilar impression.

Six cases are presented to illustrate the various measurements and to aid in differential diagnosis. The symptoms depend on the extent and degree of compression of the cervical spinal cord, medulla oblongata, or cerebellum and they may resemble those of syringomyelia, bulbar palsy, multiple sclerosis, or various other motor and sensory disturbances.—*J. Zausner, M.D.*

Soila, Pekka, and Paatero, Yrjö V. Clinical pantomography of the jaws. *Radiology*, June, 1956, *66*, 818–824. (Address: P. Soila, Central Institute of Radiation Therapy, University of Helsinki, Unioinkatu 38, Helsinki, Finland.)

Pantomography is a procedure which has been developed for the purpose of obtaining laminagrams of curved surfaces. This method employs a fixed source of radiation, while object and film are rotated on holders having equal radii and moving at equal speed through a peripheral frictional arrangement. The rather narrow roentgen beam reproduces on the film the layer of interest, which has the same linear velocity and direction of movement as the film itself. Structures outside this layer of equal linear velocity are blurred in the usual laminagraphic manner. The reproduced section, however, appears in essentially better detail than in conventional laminagraphy.

The authors call attention to the value of pantomography in examination of the jaws. Their studies have shown that this method is most useful in examination of patients who have congenital anomalies of the jaw, as a routine precedure in examination of the jaws of patients who have systemic diseases, or suffered trauma to the jaw. Furthermore, they have shown that while benign tumors and cysts are easily visualized, primary and metastatic malignant tumors do not show up well on a single pantomographic examination. Consecutive films will, however, often allow a diagnosis of malignant disease to be made. Pantomography also aids in the diagnosis of inflammatory and necrotic changes in bone, in that sequestrated bone or increased calcium within an area of healing may be more easily recognized than would be possible from a conventional film.

Pantomographic examination presents a further advantage in that the procedure is simple and easy to do on severely ill patients. Also to be noted is the fact that the same technical factors can be reproduced, and re-examination in unchanged projections is easily obtained.—*A. Ralph Watson, M.D.*

Neck and Chest

Heck, Charles V. Hoarseness and painful deglutition due to massive cervical exostoses. *Surg., Gynec. & Obst.*, June, 1956, *102*, 657–660. (From: Department of Orthopaedic Surgery, University of Illinois, Chicago, Ill.)

It is well known that pain, radiation of pain and limited neck motion occur with spurring of the margins of the bodies of the cervical vertebrae. It is extremely rare, however, to have the process progress to the extent that it causes a disturbance in deglutition and hoarseness.

The author presents 4 cases which had large cervical exostoses associated with hoarseness and dysphagia. None of the patients had a primary complaint of neck pain or radiation of pain from the neck region. There was some limitation in motion of the cervical spine in each case. Esophageal and deglutition studies by means of the barium meal were of value. One case had a carcinoma of the upper esophagus in addition to the large cervical spurs.

The course to be followed in such cases depends on many factors. Occasionally the spurs are removed. If the dysphagia becomes too great a gastrostomy can be done.—*Charles W. Cooley, M.D.*

Fischedick, O. Zur Ätiologie und Strahlentherapie des Mittellappensyndroms. (Etiology and radiation therapy of the middle lobe syndrome.) *Radiol. clin.*, March, 1956, *25*, 164–170. (Address: Kappschafts-Krankenhaus, Westerholterweg, 82, Recklinghausen [Westf.], Germany.)

In a series of 41 middle lobe syndrome cases, silicosis was verified in 17 patients. A causal relationship could not be proved in any instance and the simultaneous occurrence is believed to be fortuitous. A silicotic nodule in the middle lobe may go on to cause contraction of the entire lobe or a segment, but it does not necessarily produce bronchostenosis. On the other hand, a stenosis can be caused by enlarged calcified, silicotic nodules adjacent to the middle lobe bronchi.

Despite bronchoscopy, bronchography, and laminagraphy, no satisfactory criteria, other than a verified pathologic specimen, were elicited to differentiate benign from malignant conditions. Knowledge that a condition has existed for longer than three years suggests the benign nature of the process. One patient who had refused surgery, was referred for radiation therapy with disastrous results, for he succumbed to tuberculous cavitation.

The author makes a plea for the cautious use of radiation therapy and recommends it only when a neoplastic lesion is definitely verified.—*J. Zausner, M.D.*

Amundsen, Per, and Sörensen, Edvin. Angiocardiography in intrathoracic tumours with particular reference to the question of operability. *Acta radiol.*, March, 1956, *45*, 185–198. (From: Roentgen Department, Ullevål Sykehus, Oslo, Norway.)

To evaluate the controversial opinion of several authors concerning the value of angiocardiography in the diagnosis and prognosis of primary lung tumors, the angiocardiograms performed in the roentgen department of Ullevål Sykehus were reviewed. Out of the 180 examinations, 41 were considered of adequate technical quality to meet the present day criteria for diagnosis. The discarded cases were done prior to 1948.

The risk of angiocardiography is minimal in patients with healthy hearts. Those suspected of intrathoracic tumor usually fall into this group. In the patients reviewed, ventricular arrest was observed twice, but in both instances would probably have been overlooked had not continuous electrocardiographic and blood pressure tracings been available, since heart action restarted spontaneously. However, preparation for such a complication is essential in every examination.

Because of errors inherent in fortuitous filling defects as observed on single films, special exposures, with the knowledge of which point in the cardiac cycle each represents, are necessary. Of the 41 cases reviewed, 23 cases proved inoperable. Reviewers, without knowledge of anything about history, diagnosis or operability, selected 17 of these 23 cases as inoperable on the basis of the angiocardiographic findings. In no instances was an operable case judged inoperable on the basis of angiocardiographic study. Therefore, it seems advisable to do an angiocardiographic study on all patients deemed operable by other methods. (There is no need to do angiocardiography if the lesion is found to be inoperable by other methods of examination.)

The signs of inoperability are: (1) Occlusion of left main pulmonary artery within 1.5 cm. of its origin, or right main branch proximal to its point of bifurcation; (2) partial or complete occlusion of the great mediastinal vein; (3) mediastinal metastases demonstrated by pressure on vessels; and (4) pericardial invasion. Obliteration of the subdivisions of the main arteries is not in itself an indication of inoperability.

In addition to saving some patients unnecessary thoracotomy, the studies will give the surgeon information on the anatomic extent inoperable cases. The diagnosis of neoplasm, however, must be made on the basis of other means of examination.—*Lois Cowan Collins, M.D.*

Ringertz, N., and Lindholm, S. O. Mediastinal tumors and cysts. *J. Thoracic Surg.*, April, 1956, *31*, 458–487. (From: Clinic of

Thoracic Surgery and the Department of Pathology, Sabbatsberg Hospital, Stockholm, Sweden.)

This is a survey of 155 patho-anatomically verified primary mediastinal tumors and cysts, treated at the Clinic of Thoracic Surgery, Sabbatsberg Hospital, Stockholm, Sweden during the period 1944 to 1954. The study excludes benign and malignant esophageal tumors, metastatic tumors, intrathoracic thyroid, leukemia, Hodgkin's disease, tuberculoma, sarcoidosis, aneurysms, and parasitic cysts. The 5 most common mediastinal tumors and cysts, in order of decreasing frequency in this series, are schwannoma and neurofibroma, bronchial cysts, thymoma, adult teratoma, and ganglioneuroma. The location, gross anatomy, histology, age and sex distribution, clinical course, and result of follow-up are recorded.

About 61 per cent of the mediastinal lesions were discovered by routine mass roentgenography. Sixty-eight per cent of the benign and 23 per cent of the malignant growths in the series were found this way. By studying the annual distribution of mediastinal tumors discovered, a close agreement can be noted between the frequency of the mass roentgenography and the number of cases discovered.

This series includes several rare tumors, some being difficult to classify. The investigation has in certain details given results, partly new and partly disagreeing with previous experience. Thus, all the 3 cases of ganglioneuroblastoma ran a benign course which does not tally with the findings of Ackerman and Taylor. Among the hemangiomas there was 1 case of hemangiopericytoma and another with peculiar melanin-pigmentation, possibly a neurovascular malformation. The series also includes 1 case of plasmacytosarcoma with no signs of multiple myeloma. All tumors classified as thymomas have been diagnosed in accordance with the restrictive definition given, among others, by Seybold and associates, and in no case were there signs of extrathoracic metastasis. Only 32 per cent of the thymoma patients had myasthenia gravis (Seybold and co-workers give 75 per cent). The material finally includes 2 tumors quite unconnected with the lung or bronchial tree with a structure very similar to that of bronchial adenoma. In another similarly located, infiltratively growing tumor, the microscopic study revealed a malignant counterpart of the former. The possibility is emphasized that these tumors may be teratomas with a one-sided development, arising from the bronchial anlage. Besides 19 cases of classical bronchial cyst, the series includes 2 cases with multicystic appearance located in the costovertebral angle and with a structure similar to that of a lung anlage.—*Paul C. Olfelt, M.D.*

Vieten, Heinz, and Willmann, Karl Heinz. Röntgenuntersuchungen mit schneller Bildfolge bei Tumoren im Brustraum. (Roentgen examination of intrathoracic tumors by means of rapid serial exposures.) *Thoraxchirurgie*, Feb., 1956, *3*, 293–410. (Address: H. Vieten, and K. H. Willmann, Chirurg. Klinik, Moorenstr. B, Düsseldorf, Germany.)

In spite of improved roentgenologic procedures, particularly bronchography and angiocardiography, many problems in the diagnosis of intrathoracic tumors remain unsolved. The greatest difficulty still is the determination of operability. It is necessary to evaluate not only the morphology but also the motility of the intrathoracic organs. This can be done best by means of rapid serial exposures.

This paper does not deal with the technical factors of rapid serial exposures but only with clinical considerations.

In the diagnosis of an intrathoracic tumor usually a combination of serial exposures with contrast study is necessary. For bronchographic functional diagnosis, a slow exposure frequency is adequate (one exposure every 1–3 seconds) except in bronchostenosis where serial films during forced respiration or coughing are recommended, necessitating five or more exposures per second.

During the past few years, thoracic angiography has been found valuable in the diagnosis of intrathoracic tumors. The different types of this examination are discussed briefly (angiocardiography, angiocardiopneumography, selective pulmo-angiography, transosseal venography and arterial angiography). Direct puncture of the aorta by para-esophageal or paratracheal injection is rejected as too dangerous.

The transmitted pulsation of the barium-filled esophagus is best demonstrated by kymography. Bronchography furnishes information regarding the inspiratory function of the lungs. The angiographically demonstrable changes of pulmonary vessels are largely uncharacteristic and usually of little value in the differential diagnosis of pulmonary tumors. The authors' figure of about 35 per cent correct diagnostic results agrees with the reports by Dotter and Steinberg.

The reverse is true in cases of vascular disease such as arterio-venous malformation or aneurysm, where serial contrast study is the method of choice. This is also true of the differential diagnosis between aneurysm and mediastinal tumor.

Occasionally, angiography permits differentiation between a benign and a malignant tumor, but one should be very cautious in drawing such conclusions. Obstruction of the vena cava alone, for instance, is no definite proof of malignancy. The authors, however, emphasize one differential diagnostic sign: the presence of large and extensive anastomosis in benign obstruction in contrast to their paucity in malignant, rapidly growing tumors.

Serial angiography is of help to the surgeon, for localization and estimation of the shape and extent of a tumor and its relation to the heart and great ves-

sels. In the presence of bronchogenic carcinoma, a partial or complete occlusion of the right or left pulmonary artery will often determine operability. Pathologic changes in the venous circulation often indicate inoperability.

Finally mentioned are cardiac tumors, intracavitary and otherwise.

The paper is an interesting review, contains almost 100 references and 12 reproductions of beautiful roentgenograms of tumors of different types in pertinent cases.—*Egon G. Wissing, M.D.*

Dalith, F. Systolic expansion or aorto-diastolic displacement; a roentgenkymographic study of left atrial movements in mitral cardiopathy. *Acta radiol.*, March, 1956, *45*, 217–230. (From: Roentgen Department, Government Hospital, Tel-Hashomer, Israel.)

Systolic expansion of the left atrium has long been recognized as a significant sign in the roentgenologic diagnosis of mitral regurgitation.

The author's study is based on 64 kymographic examinations in a series of 131 cases of mitral stenosis operated on by Y. M. Pauzner. The kymograms are mainly of patients in whom "systolic expansion of the left atrium" was noted preoperatively by the radiologist and "pure mitral stenosis without regurgitant jet" was established by the surgeon by intracardiac palpation. The remainder of the cases of the material consists of cases in which no "systolic expansion" was noted and of cases in which a "regurgitant jet" was palpated.

The author concludes that the "systolic expansion of the left atrium" is caused by pulsatory displacement of the left atrium (during ventricular systole) due to the expanding aorta rather than, as generally assumed, by atrial expansion due to regurgitant blood stream from the left ventricle. The designation "aorto-diastolic displacement" is proposed for the phenomenon.—*C. Peter Truog, M.D.*

Celis, Alejandro, Kuthy, José, and del Castillo, Ermilo. The importance of the thoracic duct in the spread of malignant disease. *Acta radiol.*, March, 1956, *45*, 169–177. (From: Tuberculosis Service and the Department of Experimental Surgery, General Hospital, Mexico, D. F.)

A study of the lymphatics of the thorax was conducted by opacification of the lymphatics in 44 human cadavers, and by catheterization of the terminal portion of the thoracic duct in 47 living dogs. The initial investigation previously published was to establish a method of opacification, and subsequently the study was pursued in patients with malignant disease in order to study the status of thoracic duct in such cases and correlate the findings with autopsy findings.

With only one exception, a normal appearing thoracic duct meant no malignant cells in the duct.

In patients with obstruction of the duct, there were usually pulmonary metastases, presumably due to metastatic emboli passing through the duct before its occlusion or through new ducts created by occlusion. Obstruction of the duct leads to new pathways or collaterals which may drain directly into the venous circulation. Collaterals were not demonstrated in all cases of obstruction.

In experimentation with dogs, collateral circulation developed within fifteen days to three weeks after ligation of the thoracic duct.

The authors feel that the techniques used in these studies, both cadaver and dog, are not applicable as a routine clinical procedure.—*Lois Cowan Collins, M.D.*

Abdomen

Rawson, S. P. Some rare causes of vomiting in infancy and childhood. *Proc. Roy. Soc.*, May, 1956, *49*, 269–272. (From: Royal Hospital for Sick Children, Glasgow, C. 3 Scotland.)

The author reports the roentgen studies in 5 patients presenting with symptoms of vomiting or regurgitation of food. Two of the patients had abnormalities in the duodenal area, 1 in the upper esophagus and the other at the pharyngo-esophageal junction. In the fifth case the vomiting was related to hydrocephalus secondary to congenital atresia of the aqueduct of Sylvius.

The most unusual case was the one with a deformity of the upper esophagus where there was a diverticulum like structure originating from the posterior aspect of the cervical esophagus, which the author believes represents a variation of esophageal atresia hitherto undescribed. This was first identified following a swallowing of a coin, and subsequent barium studies following removal of the coin demonstrated this abnormality. The 2 cases of duodenal obstruction represented enterogenous cysts producing obstruction of the terminal part of the duodenum, and malrotation of the colon with adhesions producing obstruction also in the region of the ligament of Treitz.

One case had vomiting associated with gross hydrocephalus of a severe degree, with congenital atresia of the aqueduct of Sylvius. The last case was that of a newborn infant where the roentgen studies suggested a neuromuscular dysfunction of the pharyngo-esophageal junction with regurgitation through the nose and into the trachea. The exact nature of the lesion was obscure, although the lipiodol swallow demonstrated a form of achalasia at the pharyngo-esophageal junction.—*James F. Martin, M.D.*

Margulis, Alexander R., Nice, Charles M., Jr., and Rigler, Leo G. The roentgen findings in primary hepatoma in infants and children; an analysis of eleven cases. *Radiology*, June, 1956, *66*, 809–817. (Address: A. R. Margulis, University of Minnesota Hospitals, Minneapolis 14, Minn.)

The authors report the results of an analysis of the clinical and roentgen findings in 11 cases of primary carcinoma of the liver in infants and young children. Roentgenograms were studied and the changes correlated with the observation at surgery and autopsy.

On the basis of this analysis it was concluded that a presumptive diagnosis of carcinoma of the liver can be made roentgenologically in an anemic child with a growing mass in the upper abdomen. Roentgen studies make possible localization of the mass intraperitoneally by demonstrating displacement of anatomic landmarks. Usually it is possible to distinguish the kidney outline from the tumor. The duodenojejunal junction, fixed by the ligament of Treitz, is never pushed forward. The retroperitoneal portions of the ascending and descending colon and the second portion of the duodenum can be seen posteriorly in normal position. The transverse colon is displaced anteriorly. The mass of the primary carcinoma of the liver is inseparable from the liver and usually presents an undulating lower border. Calcification may be present in the mass (3 of 11 cases). A tumor in the right lobe of the liver depresses the haptic flexure and usually displaces the stomach somewhat to the left. A tumor in the left lobe produces marked displacement of the stomach to the left and may depress the splenic flexure.

It was found that in the majority of the cases, the diagnosis could be made by correlating the roentgen studies and the clinical findings.—*A. W. Sommer, M.D.*

Melamed, Myron, and Pantone, Anton M. Hematoma of the duodenum; a case report. *Radiology*, June, 1956, *66*, 874–876. (Address: M. Melamed, Department of Radiology, University of Illinois College of Medicine, Chicago 12, Ill.)

Gastrointestinal symptoms after trauma to the abdomen should lead one to consider the possibility of hematoma of the bowel. A case of hematoma of the duodenum which was demonstrated roentgenographically, with return of the duodenum to normal in one month following conservative treatment, is presented.

Roentgen signs of duodenal hematoma are: intramural tumefaction with sharply demarcated margins; narrowing or obliteration of the normal duodenal lumen; a mucosal "coil spring" pattern; an unusual collection of barium in the involved bowel segment, which may represent a mucosal ulceration; disappearance of the roentgenographic findings with reversion to normal in follow-up studies. Roentgen diagnosis is important as surgical intervention may be avoided in the absence of complete obstruction or accompanying lesions.—*Harold C. Hamilton, M.D.*

Wolf, H. G. Zur Röntgenologie der terminalen Ileumschlinge im Kindesalter. (The roentgen examination of the distal loop of the ileum in children.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1956, *84*, 432–439. (Address: Universitäts-Kinderklinik, Lazarettgasse 14, Wien IX, Austria.)

The term ileitis terminalis catarrhalis has been used to describe a disease of the lymphatic tissue in the distal ileum in children. While some authors deny the existence of such an entity, others consider it responsible for colicky pains in childhood.

The author reports on his experience with the roentgen examination of the distal ileum in children. It is primarily done by means of a barium enema and retrograde filling of the ileum. He found that the mucosal relief pattern differs with age. In very young children, increased size of the lymphatic follicles and of Peyer's plaques is noticeable. It normally causes a mottled appearance of the mucosal pattern. As the child gets older the longitudinal folds as seen in adults become more prominent.

Four cases of so-called ileitis terminalis catarrhalis are described. Roentgenologically, the markedly granular mucosal relief, delay in the passage of the barium into the cecum (when oral barium is given), edema of the folds and follicular enlargement point to the diagnosis. Clinically colic like pain and isolated tenderness of the distal loop of the ileum are usually present. The clinical course is always benign. There is no apparent connection with the regional ileitis of Crohn.

Because ACTH and cortisone in small doses are known to decrease lymphatic hyperplasia, the author gave these hormones to 4 of the patients. He believes that he could demonstrate a disappearance of the abnormal changes in two.—*Hans W. Hefke, M.D.*

Gandini, D., and Juliani, G. L'evacuazione vescicolare studiata con metodi volumetrici. (Volumetric evaluation of the emptying of the gallbladder.) *Radiol. med.*, March, 1956, *42*, 225–243. (From: Istituto di Radiologia dell 'Università di Torino, Torino, Italy.)

In recent years several roentgenologic techniques have been proposed for evaluating more accurately the degree of contraction of the gallbladder after the intake of a fatty meal. The authors have analyzed the methods proposed by Toulet; Paschetta V., *et al.*; and by Weiser.

The procedure of Weiser, considered the most simple and accurate, was adopted by the authors for

their researches in both normal and pathologic individuals. The technique is as follows: After twelve hours from the intake of the opaque substance, roentgenograms are taken in the posteroanterior and right lateral views, with the patient in erect position. With the patient in the same position, roentgenograms in the two views are again taken fifteen minutes, one hour, two hours, and five hours later. From each roentgenogram, tracings are made of the modifications of the gallbladder during the examination.

In cases affected by biliary dyskinesia, the curves representing the time in which the shrinkage of the gallbladder occurs and the degree of contraction, as compared to the findings observed in normal cases, show that the contraction takes place only for a short period. It is further shown that the changes in the volume of the gallbladder are not constant and do not follow the normal pattern.

The procedure suggested by the authors is a useful complementary examination in cases of suspected biliary dyskinesia.—*A. Govoni, M.D.*

Massenti, S., and Costa, V. Sull'uso dei mezzi di contrasto iodati idrosolubili viscosi nella peritoneografia. (On the use of water-soluble viscous iodinated contrast media in peritoneography.) *Radiol. med.*, April, 1956, *42*, 345–355. (From: Istituto di Radiologia Medica and Istituto di Anatomia Patologica, Cagliari, Italy.)

The use of water-soluble opaque substances for the roentgenologic examination of the peritoneal cavity is not new, and was advocated to better evaluate certain pathologic processes of the abdomen, generally the presence of adhesions.

In their researches, the authors have introduced into the abdominal cavity of a first group of rabbits the usual hydrosoluble substances (pielosil, 30 per cent; ioduron, 30 per cent; neopielofanina; urografin, 62.1 per cent), while the second group was injected with a highly viscous medium, ioduron B, 50 per cent (5-6-8 cc. diluted in equal amounts of sterile solution).

Roentgenograms were taken ten minutes, thirty minutes, two hours, twelve hours, and twenty-four hours after the introduction of the contrast medium, which was done in both instances under fluoroscopic control.

The animals were sacrificed at intervals of a week, two weeks, and a month from the time of injection. Histologic sections were taken from the lungs, kidneys, heart, spleen, intestine, and peritoneum.

The results in both groups for a "general peritoneography" were unsuccessful because the contrast medium diffused too rapidly in the abdominal cavity, giving only a faint visualization of the intestinal loops. The authors limited, therefore, the research to a "regional peritoneography" taking advantage of the great viscosity and the low diffusibility of the ioduron B. The results were quite successful. The contours of the intestinal loops were well outlined, especially on the ten minute film, where the contrast medium was still localized in a small area and did not spread. Of particular interest were the roentgenograms showing the contours of the bladder.

Histologic studies were done to evaluate the reactions of the various organs and these did not show any pathologic changes.

The authors are of the opinion that this type of examination of the peritoneal cavity could be safely adopted for the evaluation of limited areas of the abdomen. They feel, nevertheless, that this technique needs further investigation before being generally used.—*A. Govoni, M.D.*

Gynecology and Obstetrics

Carnevali, G., Lucarelli, U., and Paracchi, P. Possibilità e limiti della radiologia nella diagnostica delle metastasi pelviche e delle infiltrazioni parametrali da carcinoma uterino. (Pelvic metastases and involvement of the parametria from carcinoma of the uterus: indication and limits of radiologic examinations.) *Radiol. med.*, Feb., 1956, *42*, 113–139. (From: Istituto di Radiologia della Università, Milano, Italy.)

The roentgenologic examination of the female pelvic organs by induction of pneumoperitoneum was suggested in 1918 by Goetze. In the United States Stein, in 1926 and in the following years, carried out very important studies and perfected the technique of pneumogynecography.

After a period in which pneumogynecography was largely adopted, its use became less popular, and it is only after the studies done lately by Granjon, and by Lemarque, Betoulieres, Pelissier, Leenhardt, and Gary-Bobo that the importance of pneumoperitoneum in the examination of the female pelvic organs was re-evaluated.

Another technique, for the visualization of parametrial involvement from carcinoma of the uterus, was introduced by Beaux, who suggested the injection of a radiopaque substance into the cancellous bone structure of the pelvis, obtaining, thereby, a pelvic phlebography.

The present authors have adopted in their examinations pneumogynecography and/or pelvic phlebography.

The technique for the induction of a pneumoperitoneum was described in detail in a previous paper. They prefer to introduce oxygen rather than carbon dioxide, and the amount used is 1,000–1,500 cc. The examination is done with the patient lying prone and the table tilted 35° cranially. The central ray is perpendicular to the table and incident to the last vertebra of the coccyx. Three roentgenograms are taken, one in the sagittal and two in the right and left

oblique projections, respectively. In a few cases more information is obtained by taking roentgenograms with the patient lying supine.

For the pelvic phlebography the authors' preferred site for injection of the contrast medium is the tuberosity of the ischium. Twenty cc. of a 50 per cent water-soluble contrast medium is injected if only one side is used, and 15 cc. each if the medium is introduced bilaterally. Three roentgenograms in rapid succession are taken; the time elapsing between the injection and the three exposures is 8 seconds.

In 80 cases examined, the authors found pneumogynecography of great value in completing the clinical examination, obtaining more accurate data about the degree of parametrial involvement and the extension of the tumor.

Pelvic phlebography did not give very satisfactory results, and the authors feel that an involvement of the pelvic venous vessels can be demonstrated only in advanced cases, when the tumor is widely spread.

Seventeen cases are reported, and each case is illustrated with good roentgenographic reproductions and clear schematic drawings.—*A. F. Govoni, M.D.*

Genitourinary System

Eyler, W. R., Drew, D. R., and Bohne, A. W. A comparative clinical trial of urographic media; renografin, hypaque, and urokon. *Radiology*, June, 1956, *66*, 871–873. (Address: W. R. Eyler, The Henry Ford Hospital, Detroit 2, Mich.)

A total of 900 urograms of unselected patients using renografin, hypaque, and urokon in both the 50 per cent and 70 per cent solutions were studied in order to determine which gave the most diagnostic films. The reactions incident to their production were also evaluated. Renografin was used in 500 patients, hypaque in 300, and urokon in 100 patients. The results of the urokon studies have been reported in an earlier paper in this journal, and were used as a basis for comparison with these newer agents.

Only one serious reaction of anaphylactic type occurred, and that was when hypaque was used. The small number of cases in these groups makes it impossible to draw any conclusions regarding the relative frequency of this type of reaction. The less important effects of nausea, vomiting, dizziness, pruritus, hives, and arm pain were appreciably less in the renografin and hypaque groups than in the urokon series. There was a higher incidence of arm pain in the urokon group than in the others.

The diagnostic quality of the films was comparable in all of the different groups.—*Donald N. Dysart, M.D.*

Wald, Arnold M. Nephrography during routine excretory urography. *J. Urol.*, March, 1956, *75*, 572–577. (From: Department of Radiology, United Hospital, Port Chester, N. Y.)

It has been shown that the rapid intravenous injection of 70 per cent urokon will produce nephrograms by virtue of the accumulation of relatively large amounts of contrast medium in the vascular system and tubules of the kidneys a few seconds after injection. The author recommends, for routine nephrography, the following modified procedure: The usual preparation consists of a cathartic and the with-holding of food and liquids for approximately twelve hours prior to the examination. One-hundred mg. of pyribenzamine is given two hours prior to the roentgen study. A preliminary 14×17 film is made with the patient in the Trendelenburg position and without compression. A sensitivity test consisting of ½ cc. of 70 per cent urokon intravenously is then done and the patient is observed for ten minutes. Following this, the roentgen tube is centered over the kidney region and a 11×14 film is placed beneath the patient's kidneys. Twenty-five cc. of urokon 70 per cent is injected intravenously using an 18 gauge needle, in ten to fifteen seconds. Thirty seconds from the beginning of the injection the film is exposed. The patient is then given about 4 ounces of water and the subsequent intravenous pyelograms are made as indicated.

No serious reactions to the rapid injection of 25 cc. of 70 per cent urokon were noted in a series of 195 patients. However, customary reactions were a sensation of warmth, flushing, tingling sensation of the mouth or elsewhere, metallic or bitter taste and nausea. Vomiting occurred in 2 patients and urticaria in 4 patients.

In 100 consecutive routine studies by this method, good nephrograms were obtained in 64 instances and poor nephrograms in 30 instances. In 6 cases no nephrogram was obtained. The author recommends the method as an addition to the conventional procedures.—*George W. Chamberlin, M.D.*

Woodruff, J. H., Jr.; Chalek, C. C., Ottoman, R. E., and Wilk, S. P. The roentgen diagnosis of renal neoplasms. *J. Urol.*, April, 1956, *75*, 615–626. (Address: J. H. Woodruff, Jr., 1124 W. Carson St., Torrance, Calif.)

Renal neoplasms can be diagnosed, in most instances, by one or more of the various roentgen procedures. The advantages of these procedures are enumerated from the experience of the authors and from that of others as reported in the literature. The incidence and type of lesion is tabulated and correlated with the nature of the pathologic process.

Preliminary films showed positive findings in 15 of 26 cases available for study. Fourteen out of 18 excretory urograms and 19 out of 19 retrograde pyelograms exhibited the diagnostic features of renal neoplasm. Certain limitations of excretory and retrograde pyelography are indicated in such situations as

the distinction between solid and cystic tumor, tumor within cystic disease, intrarenal and extrarenal tumor, small lesions as, for example, hemangiomas or neoplasms not involving the calyceal system. Antegrade pyelography occasionally is useful in differentiating a neoplastic and non-neoplastic hydronephrosis.

Renal angiography is often helpful in differentiating cystic from solid lesions of the kidney parenchyma, small tumors which may be overlooked on pyelograms, tumor extension into the renal vein and distinction between renal and extrarenal tumors. Cortical carcinomas may fail to exhibit a characteristic vascular pattern in about 1 out of 10 cases. The pelvic tumors, adenomas and some sarcomas or metastatic carcinomas may fail to show the pathologic tumor vessels.

Presacral air injection is of value to demonstrate the peripheral extent of the renal mass and may be used in conjunction with pyelography or aortography. Any of these procedures may be employed in combination with laminagraphy.

Percutaneous puncture of renal cysts, followed by microscopic examination of the aspirated contents, contrast filling of the cyst and aortography provide a method of distinguishing renal tumors from cysts with only an occasional exception. Since 75 per cent of renal carcinomas are cortical in type and since 90 per cent of these will show abnormal vascular pattern pathognomonic of tumor, it may be surmized that approximately two-thirds of all renal carcinomas will show tumor vessels. In some instances, cysts will have tumor tissue in their wall and in other instances they will not. A cyst wall invaded by tumor should be detectable by the irregular defect on the roentgenogram made after the contrast visualization or the cytologic findings in the aspirated fluid. By the use of these combined procedures, the likelihood of an incorrect diagnosis should be considerably less than one chance in forty-two.

Other procedures which may be of value in certain instances are: contrast filling of the vena cava; nephrograms; examination of the intestinal tract for evidence of displacement; or pulmonary findings as seen on the roentgenogram.—*George W. Chamberlin, M.D.*

Davis, Hugh James, and Cian, Louis G. Positive pressure urethrography: a new diagnostic method. *J. Urol.*, April, 1956, *75*, 753–757. (From: Department of Gynecology, The Johns Hopkins Hospital, Baltimore 5, Md.)

Diverticula of the female urethra are generally conceded to be more frequent than the literature has recorded in the past. In order to demonstrate such lesions the authors have devised a special 14F Foley catheter with a 30 cc. bag and a closed distal end. This bag has an opening proximal to the distal balloon and it is passed through the urethra into the bladder. The bag is inflated with air and drawn tight against the internal sphincter. Contrast medium, such as viscous, is injected through the catheter and when it appears at the external meatus a sliding balloon is advanced against the urethra in such a manner as to occlude the meatus. An additional 3 or 4 cc. of medium is then injected and roentgenograms are made in the anteroposterior projection. A brief account of the findings of 4 patients is given. The authors state that the preliminary clinical trial of positive pressure urethrography in cases of recurrent cystitis and urethritis during the past two months have disclosed 12 new cases of suburethral diverticula which have previously been undiscovered. One of these patients has previously been cystoscoped 27 times. In two instances, urethrography demonstrated the presence of a second diverticulum which had previously been unsuspected. It would seem that the procedure is of value in the detection of these lesions in the female urethra.—*George W. Chamberlin, M.D.*

Skeletal System

Brooksaler, Fred, and Miller, J. E. Infantile cortical hyperostosis. *J. Pediat.*, June, 1956, *48*, 739–753. (From: Children's Medical Center, and the pediatric and radiology departments, Southwestern Medical College of the University of Texas, Dallas, Texas.)

The authors present a description of the clinical picture, laboratory findings, differential diagnosis, etiology, therapy and prognosis of infantile cortical hyperostosis, with a review of the literature. Eleven new cases of cortical hyperostosis are reported, four of these occurred in Negro infants. The infants were two and one-half to six months old at the time of admission to the hospital. The roentgen studies demonstrated the mandible to be involved in 8 cases; the humerus, ulna, ribs and clavicle in 4 cases each; the femur, scapula, radius, tibia and fibula in 2 cases each; and the metatarsals and metacarpals in 1 case each. The major clinical features consisted of fever, hyperirritability, pallor, and upset feeding habits. Bone involvement was identified by soft tissue swelling over the bone, fixation and tenderness to palpation.

Increased sedimentation rate and leukocytosis were noted in all cases. Anemia and an elevated serum alkaline phosphatase were present frequently.

Syphilitic periostitis, hypervitaminosis A, trauma, scurvy and malignant neoplasm are discussed in reference to differential diagnosis.

No specific therapy is indicated and the treatment is symptomatic. Hormonal therapy (ACTH and cortisone) is discussed and the authors suggest its use be limited to severe cases which lead to lasting deformity and crippling.

Infantile cortical hyperostosis is not a rare entity and should be suspected in every infant with fever, leukocytosis, hyperirritability, and swelling of the soft tissues. The diagnosis is established by roentgen

studies of the underlying bones.—*James F. Martin, M.D.*

Cruz, Miguel, and Coley, Bradley L. Aneurysmal bone cyst. *Surg., Gynec. & Obst.*, July, 1956, *103*, 67–77. (From: Bone Tumor Department of the Memorial Center for Cancer and Allied Diseases, New York, N. Y.)

Aneurysmal bone cyst is a peculiar and somewhat uncommon osseous lesion consisting of a cystic cavity, destroying the cortex of bone eccentrically and lined by a mesh of fibrous tissue and vascular spaces containing liquid nonstagnant blood.

The etiology is unknown. One author reported associated trauma in 61 per cent of the cases.

The lesion, being subperiosteal, appears surrounded by a thin shell of bone giving a specific roentgen image.

The gross pathology is a cystic cavity when the protective shell of bone is removed. Blood wells up constantly making removal difficult. Microscopically, there is fibrous tissue with long, fusiform cells with elongated nuclei. In addition, hemosiderin-laden phagocytes and giant cells are observed. This condition has been the greatest cause for confusion with true giant cell tumors. The giant cells do not form a homogeneous pattern as in true giant cell tumors and in addition, the latter lacks the characteristic blood-filled vascular spaces.

The treatment is predominantly surgical, but if located in a position where surgery is not feasible, roentgen therapy may be used.

The authors report 20 cases with characteristic clinical, roentgenologic and microscopic features of the disease.—*C. Peter Truog, M.D.*

Holsti, Lars R. Osteochondritis ischiopubica. *Acta radiol.*, March, 1956, *45*, 178–184. (From: Roentgen Department, Orthopaedic Hospital of the Invaliidisäätiö [Invalidstiftelsen], Helsingfors, Finland.)

The variations in appearance of the ischiopubic junction in the growing child make differentiation between normal and inflammatory disease difficult. Mild symptoms (pain, muscle spasm, absence of fever) in conjunction with decalcification, rarefaction, and cystic areas of absorption at the ischiopubic junction, with spontaneous recalcification a few weeks or months later, establish the diagnosis. At least for the time being, there are no reliable criteria from which it is possible to differentiate roentgenologically between osteochondritis ischiopubica and cases of normal irregular mineralization. The importance of the condition is in cognizance of its occurrence in order to differentiate it from a more serious disease.

Fifteen cases are reported and it is suggested that overexertion may be a causative factor.—*Lois Cowan Collins, M.D.*

Blood and Lymph System

Stein, Joseph, Poppel, Maxwell H., Krueger, Erich G., and Malsky, Stanley, Portable shield for radiation protection during angiography. *Radiology*, June, 1956, *66*, 887–889. (Address: J. Stein, Veterans Administration Hospital, Bronx, N. Y.)

A new protective shield for use during angiography is described, consisting of 3 sections of lead-impregnated rubber, with the center section mounted on a rotating drum. This self-contained center section can be moved up and down depending on the individual patient's height, and contains a square lead-glass partition for observation of the patient during the examination.

It is designed to be used as a supplement to the ordinary lead apron, and has been found to be much more flexible in its use than conventional portable lead-lined shields. It also reduces the potential overdosage to exposed parts, such as the hands.

The dosage received by the examiner using both the new protective shield and a conventional apron was found to be 10 milliroentgens compared to 109 milliroentgens with the apron alone.

Several photographs and a construction diagram are included.—*Charles L. Stevenson, M.D.*

Aurig, G., and Radke, H. Die Bedeutung der Aortographie für die Diagnostik der abdominalen Aortenaneurysmen. (The importance of aortography in the diagnosis of abdominal aortic aneurysms.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, June, 1956, *84*, 661–670. (Address: G. Aurig, Zentral-Röntgen-Institut, Städtisches Krankenhaus im Friedrichshain, Leninallee 171, Berlin NO 18; H. Radke, Universitäts-Röntgen-Institut, Liebigstr. 20a, Leipzig, Germany.)

Because of the rapid progress in vascular surgery, aortography has become increasingly important. Injection of the aorta proximal to the abdominal aneurysm is made after a preliminary film has indicated the site of the aneurysm either by calcification within its walls or by the appearance of a mass in the lumbar region. Such injection will localize the aneurysm, give information about its form and size, elicit characteristics of the aortic wall, furnish data of the hemodynamics of the abdominal vascular system, and by means of serial films determine the function of neighboring organs, particularly the kidneys. The ideal level for injection is at the twelfth dorsal vertebra or just above the celiac axis. More than one entry into the aorta is not desirable.

The differentiation between true and false aneurysms is difficult and only of academic interest. A dissecting aneurysm may be recognized by the minimal degree of dilatation, the smooth contour of the aortic

lumen, the relatively poor filling with contrast material, the occasional decrease in caliber of the aortic lumen (because of the intramural thrombosis), and the participation of the pelvic vessels in similar alterations. Mural thrombi may be recognized by the spotty irregularities of the contrast column. Kidney function can be determined by the resultant nephrogram, or its absence in a nonfunctioning kidney.—*J. Zausner, M.D.*

Angei, A., Napoleone, F., and Spanu, G. La splenoportografia nella diagnostica della idatidosi epatica. (Splenoportography in the diagnosis of hydatid cysts of the liver) *Radiol. med.*, March, 1956, *42*, 243–250. (From: Istituto di Radiologia Medica della Università di Cagliari and Divisione Chirurgica dell' Ospedale Civile di Cagliari, Cagliari, Italy.)

The roentgenologic diagnosis of hydatid cyst of the liver is frequently difficult to make, especially where the cyst is completely surrounded by the hepatic parenchyma.

In 5 cases in which the presence of an echinococcus cyst of the liver was suspected, the authors adopted the percutaneous splenoportal venography.

The roentgen findings can be summarized as follows: (1) Absence of opacification of the area occupied by the cyst; (2) upward displacement with or without thinning of the right ascending branch; (3) upward or downward displacement of the portal vein; and (4) increased vascularity of the left lobe of the liver with filling of the smaller secondary branches when the cyst is of a good size. In one case, in which the cyst was located between the right and the left lobes of the liver, the splenoportograms showed good vascularity of the inferior part of the right lobe, with less filling of the upper and external parts where only the main branches were opacified; external and downward displacement of the right hepatic branch and particularly of the ascending radicles; and scanty visualization of the left hepatic radicles with opacification of the middle and left areas of the liver.

The findings, besides showing the intrahepatic mass, were in all cases of great importance for the useful information they gave the surgeon regarding the type of intervention needed.—*A. Govoni, M.D.*

RADIATION THERAPY

Hunt, Howard B. Comparative radiotherapeutic results in carcinoma of the endometrium as modified by prior surgery and post-irradiation hysterosalpingo-oophorectomy. *Radiology*, May, 1956, *66*, 653–666. (Address: The Radiologic Center, 3612 Cuming St., Omaha 3, Nebr.)

The author presents an analysis of the radiotherapeutic results in 110 patients with endometrial carcinoma. All cases were followed five years or more. Staging as described in the Stockholm report was employed. No Stage 0 cases were included in this study.

The absolute five-year survival rate for this series of 110 consecutive patients with endometrial carcinoma referred for radiation therapy, was 60.9 per cent, being 82.3 per cent for Stage I cases and 26.2 per cent for Stage II. Patients with early, well differentiated lesions treated primarily by surgery and not referred for radiation therapy were excluded from the series.

Primary radiation therapy, consisting of fractionated radium application in multiple intrauterine capsules and vaginal applicators, administered concurrently with external roentgen therapy, gave a five-year survival rate of 12 per cent for Stage II cases and 77.8 per cent for Stage I cases. Radiation therapy alone was limited to cases inoperable because of nonresectable and metastatic cancer, poor operative risks, and patients refusing surgery. Subtotal or total hysterectomy, followed within one month by intravaginal radium and external roentgen therapy gave a five-year survival rate of 70.8 per cent. Intravaginal radium is considered the most essential component of postoperative radiation therapy.

Eighteen selected patients were treated by combined radium and roentgen therapy, followed by hysterosalpingo-oophorectomy after six to twelve weeks. All of these have survived five years or more. The author considers this the optional treatment.—*A. W. Sommer, M.D.*

Amdrup, E., and Knudsen, G. Ultrasoft roentgen rays in the treatment of hemangiomas; a follow-up examination of 400 cases of strawberry marks and port-wine stains. *Radiology*, June, 1956, *66*, 825–834. (Address: E. Amdrup, Kommunehospitalet, Copenhagen K, Denmark.)

It is generally recognized that hemangiomas should be treated as early as possible, preferably during the first year of life, to obtain the best results. The authors report in this paper on the results of the treatment of 400 cases of strawberry marks and port-wine stains. The hemangiomas were clinically classified into 2 main groups: Flat hemangiomas which include nevus araneus (stellate or telangiectatic angioma), nevus simplex, and nevus flammeus (nevus vinosus or port-wine stain), and the elevated hemangiomas which include strawberry marks and cavernous hemangiomas.

Radiation with a half-value layer of less than 2 mm. of skin was generally used, with 30 kv. and a half-value layer of 1.35 or 1.43 mm. of skin being used most frequently. Flat hemangiomas were frequently treated with a still lower voltage, usually 20 kv. with a half-value layer of 1.01 mm. skin. A dose of 800 to 1,200 r was given in one sitting and was not repeated until an interval of at least 4 months had

elapsed, and more than 3 exposures were never given. Flat hemangiomas were irradiated directly, without compression. Elevated lesions were compressed, during the exposure, by a sheet of roentgenographic film, from which the light-sensitive emulsion has been washed off.

There were 315 strawberry mark lesions in this study and of this number 212 (67.7 per cent) were considered to have excellent results, which consisted of complete disappearance of the lesion with no or slight remaining scar. Seventy-four (23.7 per cent) had good results with a slight visible residual lesion or complete disappearance with a distinct, non-disfiguring scar. Twenty-seven (8.6 per cent) had less satisfactory results with the lesion being either unchanged, changed with a disfiguring residual lesion, or having completely disappeared with a disfiguring scar. Cosmetic results were most satisfactory when the lesions were small and the impression was gained that the softer qualities of radiation produced greatly superior results.

Eighty-seven of the lesions in this study were port-wine stains. Fifty-nine patients were satisfied with the result, while 17 were dissatisfied, not with residual scarring, but with failure of the hemangioma to disappear completely. Clinically 42 (48.3 per cent) were considered to have excellent results; 25 (28.7 per cent) had good results, and 19 (21.8 per cent) had less satisfactory results.

The history of the use of ultrasoft roentgen rays is given and the equipment used for this type of treatment is discussed.

An excellent bibliography is presented at the end of the article.—*Donald N. Dysart, M.D.*

Trübestein, Hermann. Beitrag zur Behandlung der Lymphogranulomatose. (Contribution to the treatment of lymphogranulomatosis.) *Strahlentherapie*, April, 1956, *99*, 526–535. (From: Universitäts-Röntgeninstitut, Frankfurt a. M., Germany.)

Of 312 patients with histologically verified lymphogranulomatosis, 51.6 per cent were males, 48.4 per cent females, and 54 per cent were in their second and third decades of life. The youngest patient was a 4-year old boy; the eldest a 78-year old man.

These patients were treated with radiation alone, or with radiation in combination with drugs. Those who received more than 2,000 r tumor dose, whether or not with drug therapy, had a longer survival time, the five-year survival being almost doubled. Patients treated with a combination of radiation and drugs did slightly better than those treated with radiation only, provided drug therapy was instituted so as not to interfere with delivering the large tumor dose of radiation.

This study lends slight support to the impression that the lymphogranulomatosis runs a less malignant course in females. Further, the author has the impression that a lymphogranulomatosis appearing first in inguinal lymph nodes (as opposed to in the cervical lymph nodes) is more quickly fatal; and that a lymphogranulomatosis appearing first in the retroperitoneal lymph nodes is the most malignant. The importance of early treatment is again emphasized.—*Henry G. Moehring, M.D.*

Martin, Charles L., and Martin, James A. Carcinoma of the posterior tongue treated with radiation. *Radiology*, June, 1956, *66*, 835–841. (Address: C. L. Martin, 3501 Gaston Ave., Dallas 10, Texas.)

In this article, the authors present an excellent discussion of some of the problems which must be met in the diagnosis and treatment of carcinoma of the base of the tongue. Theories as to the etiology of carcinoma of the tongue are reviewed, and it is pointed out that although syphilis has often been considered a commonly associated disease, this has not been found to be true in their series.

A total of 120 cases of primary carcinoma of the tongue have been treated. Forty of these patients had lesions involving the posterior third of the tongue, and it is this group which is considered in the present study.

All patients were treated primarily with low-intensity radium needle implantation of the primary tumor. As a rule, lesions located in the true base of the tongue were treated by the vertical implantation of needles containing 2.4 mg. of radium distributed in 4.0 cm. of active length. Tumors of the posterior lateral border and extensions into the floor of the mouth and sides of the pharynx were implanted with needles containing 1.33 mg. of radium in 1.5 cm. of active length. It is stated that prompt healing and the prevention of sloughs depend on the production of proper needle patterns in these irregular areas, and that a certain amount of clinical judgement and experience are essential. Since palpation of the lesion under anesthesia is usually superior to visualization mapping the outlines of these tumors, preconceived needle patterns are often changed at the operating table after a proper examination is carried out. Lymph node metastases, when present, were treated by interstitial radium implants combined with heavily filtered roentgen rays with conventional 220-kv. equipment. Radical surgery as a primary approach was not used in any instance. The importance of symptomatic and supportive care is emphasized.

It is significant that the complications of treatment in this series were considered, with one exception, to be relatively minor. There was only one instance of mandibular osteonecrosis and fistula formation. This complication eventually required partial mandibular resection, but one should also note that this patient was well eight years after treatment of the tongue lesion.

The five year salvage of the group herein reported was 38 per cent. This result compares favorably with

a five year salvage of 33 per cent obtained for the authors' entire group of 120 cancers involving all portions of the tongue treated with a similar technique.

The survival rates reported by other authors for carcinoma of the posterior tongue are generally lower than those for lesions involving the anterior tongue. This appears to be true for all methods of therapeutic approach. Although the present series is small, the absolute salvage of roughly one in three compares favorably with results obtained in other tongue areas and indicates that the low-intensity radium needle technique offers certain advantages—*A. Ralph Watson, M.D.*

Ng, Elmer, and Low-Beer, Bertram V. A. The treatment of Wilms' tumor. *J. Pediat.*, June, 1956, *48*, 763–769. (From: Department of Radiology, University of California School of Medicine, San Francisco, Calif.)

The authors discuss nine additional cases of Wilms' tumor seen at the University of California Hospital from 1944 to 1955. They review the results in the total series of twenty-seven cases seen since 1926. The average age for this group was 4.8 years.

The symptoms as a rule did not appear until the tumors had become quite large and easily palpable. The most frequent complaint was a mass without associated discomfort in the abdomen. Fever was present in three cases. One patient demonstrated a microscopic hematuria but no gross hematuria was noted.

The roentgen studies in the present group of nine patients showed calcification in only one.

The authors tabulate the results of treatment for Wilms' tumor as follows: Nephrectomy alone, 75 per cent survival; nephrectomy plus postoperative irradiation, 57 per cent survival; preoperative irradiation plus nephrectomy plus postoperative irradiation, 87.5 per cent survival. They describe preoperative irradiation in which the plan has been to deliver a midline tissue dose of 2,500 r in a period of from three to four weeks. Nephrectomy was not carried out until three or four weeks after treatment in order to allow for the maximum effect of the irradiation on the tumor. A second similar course of radiation therapy was carried out one to two weeks after nephrectomy.

The authors conclude that further trial of preoperative irradiation, nephrectomy, and postoperative irradiation in unselected cases appears warranted.—*James F. Martin, M.D.*

Lochman, David J., and Morris, Roger S. The treatment of lung cancer with radiation and radiomimetic drugs. *Radiology*, June, 1956, *66*, 842–844. (Address: D. J. Lochman, Department of Radiology, University of Chicago, Chicago 37, Ill.)

The authors report the results of a study to determine relative effectiveness of several methods of treatment of pulmonary carcinoma. Thirty-eight patients constitute the series on which this study is based. In all except 12 obviously inoperable patients, exploratory thoracotomy was done, with partial resection of the tumor (19 cases) or pneumonectomy (7 cases). Patients with evidence of generalized carcinoma were not included in the series. Eighteen patients were treated by irradiation alone. Twenty patients received both chemotherapy and irradiation. Six patients received nitrogen mustard intravenously initially and 6 following irradiation. Triethylene melamine was administered to 6 patients and 2 received triethylene phosphoramide.

Radiation was given at 250 kvp., h.v.l. 1.5 mm. Cu, and focal skin distance of 50 cm. The treatment was directed to both the primary tumor and the mediastinum. A tissue dose rate of about 1,000 r per week was maintained. Six patients received a tumor dose of over 4,000 r and 12 received doses below 4,000 r.

It is concluded that irradiation alone gives substantial symptomatic relief, but high dosage does not increase survival time over moderate dosage. The clinical results produced by a combination of chemotherapy and irradiation in primary lung cancer are not superior to those obtained with irradiation alone, although chemotherapy in combination with high-dose irradiation is followed by greater objective evidence of tumor destruction.

Tables are included to show average survival time, roentgenographic evidence of tumor regression, and duration of palliation.—*A. W. Sommer, M.D.*

Orton, K. F. Rotation therapy with a 2 MeV Van der Graaff generator. *Brit. J. Radiol.*, April, 1956, *29*, 186–192. (From: Sheffield National Centre for Radiotherapy, Sheffield, England.)

Equipment at Sheffield for the use of rotation techniques with a 2 mev. Van de Graaff accelerator is described. An ingenious device for reproducing treatment technique is shown, and directions for its use are given. An instrument for calculating dosage with rotation therapy is also described.—*R. Kenneth Loeffler, M.D.*

Greene, D., and Tranter, F. W. Dosage data for 4,000,000 volt x rays. *Brit. J. Radiol.*, April, 1956, *29*, 193–195. (From: M.R.C. Betatron Research Unit, Christie Hospital, Manchester 20, England.)

Output and depth dose data are presented for the 4 mev. linear accelerator which has been in use at the Christie Hospital in Manchester since May, 1954. The focal spot is 6 mm. in diameter. A conical aluminum filter is used to reduce the variation in intensity across the roentgen ray beam. A field of 24 by 30 cm. can be obtained at 1 meter. With the compensating filter, an output of 120–130 r/min. at 1 meter can be obtained though the machine is customarily operated at 100 r/min. for therapy. There is an over-all varia-

tion of about 10 per cent in output for field sizes of 20 to 400 cm.²

The depth doses vary less than 2 per cent for a given area among square fields and rectangles of up to 3:1 elongation. For varying focal-surface distances, depth doses are related by the inverse square law to within 1 per cent. The maximal dose is from 0.8 to 1.2 cm. below the surface. The dose at 10 cm. is 57 per cent of the maximum for a 4 by 4 cm. field; 67 per cent for a 20 by 20 cm. When the beam enters bolus material obliquely, the central ray depth doses are the same as those obtained at normal incidence. For any other ray, the depth dose may be calculated from the normal incidence depth dose, corrected for the change in focal-skin distance resulting from the change in angle of incidence. These relatively simple physical relationships result from the greater tendency for forward scatter with 4 mev. as opposed to lesser energy radiation.—*R. Kenneth Loeffler, M.D.*

Morrison, R., Newbery, G. R., and Deeley, T. J. Preliminary report on the clinical use of the medical research council 8 MeV linear accelerator. *Brit. J. Radiol.*, April, 1956, *29*, 177–186. (From: Radiotherapeutic Research Unit of the Medical Research Council, and Radiotherapy Department, Hammersmith Hospital, London, England.)

Two hundred and fifty-seven patients were treated with roentgen rays generated by the 8 mev. linear accelerator at Hammersmith Hospital in the first year after completion of physical tests in August, 1953. The skin erythema dose is similar to that from radium gamma rays when a wax layer is placed over the skin to bring the maximum dose to the skin surface. There is no appreciable difference in effect on the growth of the bean root between 8 mev. and radium radiations. The maximum dose is at 2 cm. The dose at 10 cm. is 70 per cent of the maximum for a 50 cm.² field, 72 per cent for a 200 cm.² field.

The physical advantages of megavoltage radiation over 250 kv. roentgen rays are listed, and the methods and techniques of treatment planning described. Early experiences in the treatment of patients with advanced disease have shown satisfactory tumor regression with only slight skin and mucosal reactions. Many lesions of the mouth, throat and larynx are now treated with the megavoltage radiation.—*R. Kenneth Loeffler, M.D.*

Uhlmann, Erich, M., Hsieh, Charles L., and Lootens, C. Louis. The linear electron accelerator as a source of fast electrons for cancer therapy. *Radiology*, June, 1956, *66*, 859–870. (Address: E. M. Uhlmann, Tumor Clinic, Michael Reese Hospital, Chicago 16, Ill.)

Recent developments in equipment for the production of free beams of fast electrons in the multimillion volt range have made possible their utilization in medical therapy. At the Tumor Clinic of Michael Reese Hospital, Chicago, Illinois, the authors have been using a linear accelerator with an energy of 40 mev., for over a year. Prior to this they had a 20 mev. betatron at their disposal. Their experimental results with the 40 mev. equipment are to be correlated and published later, and this article is mainly a comprehensive description of the apparatus and facility. The reader is urged to consult the original article for the details.

The essential components of the accelerator are: (1) the accelerator tube, through which both electromagnetic waves and electrons propagate themselves. This tube is a ten foot long disk-loaded wave guide made from oxygen-free, high conductivity copper tubing, with the inside highly polished and plated with pure gold. The disks are of selenium copper; (2) the microwave power source (magnetron oscillator) and the klystron amplifier which excites the proper wave inside the tube; (3) the main high voltage supply, which furnishes pulsed high voltage for the operation of the klystron amplifier; (4) the electron gun, which produces bursts of high velocity electrons; (5) the trigger generators for synchronization of pulsers; (6) the various vacuum systems for evacuating the klystron, accelerator tube, and magnet chamber; (7) the interlocks for protection of personnel and instruments; (8) the magnet system for control of energy direction and size of output electron beam; (9) the monitoring system for measuring the beam intensity and control of the desired dosage to patients.

The accelerator has definite advantages over the betatron for medical therapy. It operates quietly, has a straight-forward linear beam, and requires no special gadgets for the liberation of electrons from the apparatus. Maintenance is simple, and the apparatus is flexible enough to be used for even very sick patients. A wide variety of field sizes are possible because of the magnet system, allowing easy individualization of treatment. Also the gamma ray background at the target is so small that it presents no special problems or hazard.—*Charles L. Stevenson, M.D.*

Becker, J., Weitzel, G., and v. d. Decken, C. B. Die Gittermethode bei der Strahlenbehandlung mit schnellen Elektronen. (The grid method in radiation therapy with fast electrons.) *Strahlentherapie*, Feb., 1956, *99*, 213–220. (From: Czerny-Krankenhaus für Strahlenbehandlung der Universität, Heidelberg, Germany.)

With a one centimeter thick iron or lead grid and a fast electron beam of 15 mev. from a betatron, the intensity of the beam becomes homogeneous at a tissue depth of about 4 cm. The grid consists of 7 mm. holes bored in the metal plate so that the ratio

of unshielded to shielded area is 40:60. Clinical observations made thus far indicate that the skin is extraordinarily spared, even in the face of previous radiation damage.

The authors promise a subsequent report on a similar technique with ultrahard roentgen rays.—*Henry G. Moehring, M.D.*

RALSTON, EDGAR L. (Philadelphia, Pa.) Fracture of the femoral neck following irradiation of the pelvis. *Surg., Gynec. & Obst.*, July, 1956, *103*, 62–66.

The incidence of femoral head fracture following pelvic irradiation for carcinoma has been reported as varying between 1 to 2 per cent of cases. This incidence is high enough to suspect any person who complains of hip pain following such treatment to have a fracture of the femoral neck. The fracture may not be apparent on the first roentgen examination and be seen a few weeks later.

The results of treatment after an early diagnosis are superior to those after delayed diagnosis.

The choice of reconstruction procedure will depend on factors presented by each case.—*C. Peter Truog, M.D.*

BUCHMANN, ERICH. Darmschäden durch intravaginale Körperhöhlenrohrbestrahlung. (Intestinal injuries from transvaginal irradiation.) *Strahlentherapie*, Jan., 1956, *99*, 39–46. (From: Röntgen- und Geschwulstinstitut des Rudolf Virchow-Krankenhauses, Berlin, Germany.)

Three patients' clinical courses illustrate three less well-known types of radiation injury to the intestine from transvaginal irradiation. These injuries are probably more common than the oft-mentioned rectovaginal fistulae.

(1) A 46 year-old patient developed fatal peritonitis following perforation of a *radiation ulcer in the ileum*. She had had a Wertheim hysterectomy three and one-half years before, and both external and transvaginal roentgen irradiation within one and one-half years of her death.

(2) A 52 year-old patient developed a radiation *stricture of the sigmoid*, relieved surgically, after external and transvaginal irradiation for carcinoma of the cervix. Almost twenty years before she had had pelvic surgery for treatment of a tubal pregnancy.

(3) A 57 year-old patient developed *rectal stenosis and parametrial fibrosis* eight months after external and transvaginal radiation therapy for carcinoma of the cervix.

The following prophylactic measures should decrease the incidence of intestinal damage: Transvaginal irradiation should not be undertaken if a pretreatment examination of the colon shows evidence of intestinal fixation by adhesions, or an otherwise disadvantageous position of the colon in relation to the intracavitary beam. A previous history of pelvic inflammation or surgery requires a cautious approach to transvaginal therapy. With a retroflexed, or thin-walled uterus, the regional dose of radiation is sufficiently raised to endanger the gut. Frequent change of the patient's position during radium therapy is advantageous. To avoid excessive elevation of the uterus, vaginal packing should be more circular than longitudinal. The transvaginal tube itself should not be inserted to the point of thrusting vaginal vault upward into contact with loops of small bowel. Intestinal irritation during therapy is a signal to interrupt treatment or to protract treatment more.—*Henry G. Moehring, M.D.*

BAŠIĆ, MARKO, and WEBER, DANICA. Über intrauterine Fruchtschädigung durch Röntgenstrahlen. (Intrauterine fetal damage by roentgen rays.) *Strahlentherapie*, April, 1956, *99*, 628–634. (From: Allgemeines Krankenhaus "Dr. Stojanović," Zagreb, Yugoslavia.)

In July, 1950, this mother underwent a mastectomy for carcinoma. She did not menstruate after the operation. In September 1950, skin metastases were present in the mammary region. Radiation castration then, consisted of 600 r to 10×15 cm., right and left, anterior, lower abdominal ports and 300 r to a 24×24 cm. posterior port. The radiation was generated at 180 kv., 10 ma., and filtered through 0.5 mm. of Cu at a 40 cm. f.s.d. Shortly after this treatment, the mother became aware of lower abdominal enlargement and pelvic examination demonstrated a pregnancy of about 4 months' duration. Subsequently she received additional radiation to axillary and supraclavicular regions, developed extensive visceral metastases, delivered a live infant in Feb., 1951 (during the ninth month of pregnancy), and died.

The female infant weighed 1,900 gm. and was 45 cm. long. She stayed in the hospital for three months before being transferred to a children's home. Relative underdevelopment of the lower portion of her body and a cephalic circumference of 32 cm. (vs. normal of 34 cm.) were noted. The child re-entered the hospital at the age of three years. Then the examinations showed severe intellectual and physical underdevelopment. The child was microcephalic with external hydrocephalus and porencephaly; she spoke an occasional unintelligible word, but understood no words; she had not yet reached the development of a year-old child and was classed as an idiot. General atrophy, including skeletal underdevelopment, was most evident in the lower extremities, more on the left than the right. Motor disturbances and minor ocular abnormalities were present. The skin showed pigmentary abnormalities.

Since the abnormalities of the nervous system were so prominent and the physical defects were asym-

metric, they are counted the result of radiation damage. When the mother's pregnancy was discovered, the radiologist recommended therapeutic abortion which the gynecologist refused to perform because the pregnancy was so far advanced.

The authors advise eugenic, therapeutic abortion in situations like this. Further, they feel that attempts to produce abortion by radiation are contraindicated and cite Doctor D. P. Murphy's report (*Am. J. Obst. & Gynec.* 1929, *18*, 179) that 34 per cent of 74 women irradiated during pregnancy bore malformed children, without aborting.—*Henry G. Moehring, M.D.*

Adler, Howard, and Kaplan, Gustave. Improvement of osseous changes in the sella turcica following irradiation for a pituitary tumor; a case report. *Radiology*, June, 1956, *66*, 856–858. (Address: H. Adler, Veterans Administration Hospital, Bronx 68, N. Y.)

An unusual example of improvement of osseous changes in the sella turcica following radiation therapy for pituitary tumor is presented. Roentgenograms of the skull and the hands showed the characteristic changes of acromegaly and there was clinical and laboratory evidence of hypopituitarism. The sella was enlarged, with a vertical measurement of 15 mm. and an anteroposterior diameter of 21 mm. The diagnosis, not confirmed by histopathologic study, was that of combined eosinophilic and chromophobe adenoma of the pituitary gland.

Roentgen therapy was administered. A tumor dose of 3,000 r was delivered to the sella turcica in a period of four weeks. Following treatment, the patient improved subjectively and objectively. Roentgenograms of the skull, made about one and one-half years after completion of the treatment, disclosed a striking change in the sella turcica. The vertical measurement was 11 mm. and the anteroposterior diameter was 16 mm. The sellar floor, posterior clinoids, and dorsum sellae showed evidence of reossification.—*A. W. Sommer, M.D.*

RADIOISOTOPES

Reilly, W. A., Helwig, Harold L., and Scott Kenneth G. Blood-volume measurements in cancer using the Cr^{51} red-blood-cell tagging method. *Cancer*, March-April, 1956, *9*, 273–276. (From: Radioisotope Unit, Veterans Administration Hospital (Fort Miley), and the Department of Radiology, University of California School of Medicine, San Francisco, Calif.)

The anemia associated with malignant tumors has been investigated in rats and humans to determine whether this is due to red cell destruction or increased plasma volume. Cells are tagged with Cr^{51} and the activity measured with a scintillation counter.

In rats inoculated with a transmissible fibrosarcoma, there is an increase of plasma volume and a slight increase in red cell mass. Generally, in 175 cancer patients the red cell mass is lower and the plasma volume is greater than normal and, while the average whole-blood volume is not significantly changed, there is an increase in leukemia, carcinoma of the stomach, esophagus and colon, and a decrease with nonmetastatic cancers. The hematocrit is, in all cases, lower than normal.—*Raymond S. Quick, B.S.*

Berg, Harold F., and Christophersen, William M. An experimental study of intramammary injection of Au^{198}. *Ann. Surg.*, Jan., 1956, *143*, 92–97. (From: Departments of Surgery and Pathology, University of Louisville, School of Medicine, and Jewish Hospital Division of Louisville Medical Center, Louisville, Ky.)

Interstitially injected colloidal gold is phagocytized and collected in the lymph nodes of the drainage area of the injection site. To explore the possibility of use of radioactive colloidal gold as an adjunct of present radiation therapy, studies were done on interstitial injection of Au^{198} in the superior mammary glands of dogs.

Following a single injection of 2 mc of Au^{198} good uptake in lymph nodes occurred within three hours demonstrating that rate of uptake was sufficiently rapid in view of the half life of 2.7 days. Sites of uptake were the axillary and latissimus dorsi lymph nodes on the same side as the injection and the internal mammary lymph nodes on both sides. It was demonstrated that the Au^{198} crossed to the opposite internal mammary chain through deep lymphatic connections. Au^{198} injected into the intercostal muscle at the parasternal region produced high uptake in mediastinal and internal mammary lymph nodes.

To determine local tolerance to injection, 20 to 85 mc of Au^{198} in single doses were given. All animals with these high single doses developed severe local reaction and several showed local sloughs with doses over 50 mc. The lymph nodes of all of them exhibited marked irradiation effect.

In view of this, fractionated doses of 2 mc each week for a period of from two to twenty-four weeks were given to a series of dogs. In general, these animals tolerated the fractionated dosage schedule better than the single large dose. The effects on lymph nodes were not as marked or as diffuse as with the single large dose. Larger fractionated doses of 10 mc weekly, were given and these produced severe local reaction with no greater effect on the lymph nodes than a single 10 mc dose would produce.

Doses of 10 mc or greater produced radiation effect in lymph nodes which picked up the radioactive colloid. The effect varied considerably in degree and there was also often a patchy distribution of effect

within the lymph node. Doses in the range of 50 mc which were sufficient to obtain complete lymph node necrosis were not well tolerated locally. Patchy intranodal distribution is apparently due in part to distance of the lymph node from the site of injection and also to blocking of afferent lymph channels from previous infections or other processes.—*Robert W. Emerick, M.D.*

Bulkley, George J., Cooper, John A. D., and O'Conor, Vincent J. Present status of treatment of carcinoma of prostate with radioactive materials. *J. Urol.*, May, 1956, *75*, 837–845. (Address: G. J. Bulkley, 720 N. Michigan Ave., Chicago 11, Ill.)

On the basis of animal experiments it has been shown that radioactive gold, phosphorus and yttrium are apparently safe to inject directly into malignant prostatic tissue and are capable of destroying such tumor tissue, as well as some regional lymphatic tissue. The destruction of tissue following injection is dependent upon a uniform distribution of the radioactive colloidal material, since the beta rays have a range of only a few millimeters.

The authors present their clinical experience over the past two and one-half years. using all three of these materials in the treatment of carcinoma of the prostate. Biopsies were obtained either through the Silverman needle or transurethral resection, and most of the patients had the material injected perineally using multiple needles introduced into the perineum and guided to various portions of the tumor mass by a finger in the rectum. A dose of about 2 mc per gram in the case of gold, and 1 mc per gram in the case of phosphorus and yttrium was used.

Total doses of 45 to 180 mc of radioactive gold have been injected into 34 patients; of these 15 are living with clinical improvement, 10 are living without benefit and 9 have died of their disease.

In 5 patients who had radioactive chromic phosphate injection by the perineal method in doses ranging from 21.5 to 39 mc, there was very little change noted on rectal palpation following the treatment.

The authors point out that a good number of the patients included in this series already had extensive metastatic carcinoma and could not be expected to obtain more than temporary local benefit from the injections. These patients frequently had bilateral orchiectomy at the time of the gold injection, so that their evaluation could not be satisfactorily determined. They are inclined to feel somewhat less enthusiastic about the treatment, since a careful study of this series of patients has shown that only about one half have been benefited by interstitial irradiation. They noted that the lymph node pick-up of radioactive material seemed to be less then in their experimental experience, probably due to blockage of the lymphatics by carcinoma.

Urinary levels of radioactive material have indicated that in some cases, as much as one-third of the injected dose is lost in the urine during the first forty-eight hours. Such urinary loss is greater in the small prostatic carcinoma because of the difficulty of holding a small amount of fluid within a restricted area. It was also noted that blood levels of isotope reached a peak within three minutes following injection and in some instances, were surprisingly high. One patient, who had thrombocytopenia and suppression of bone marrow function, was found to have 28.7 per cent of the total dose of 33 mc of radioactive chromic phosphate circulating in his blood. A careful technique is necessary to prevent direct injection in the blood stream and also for maintaining a close check-up on the amount of material escaping into the circulating blood.—*George W. Chamberlin, M.D.*

Wheeler, H. Brownell, Jaques, William E., Allen, Marshall B., Soltes, Maury, O'Conor, Vincent J., Jr., and Black, Harrison. Mediastinal lymph node irradiation with radioactive gold. *Surg., Gynec. & Obst.*, Feb., 1956, *102*, 166–176. (From: Laboratory for Surgical Research and the Department of Pathology, Peter Bent Brigham Hospital, Harvard Medical School, Boston, Mass.)

In order to determine the feasibility of the use of radioactive colloidal gold as an adjunct to usual therapy of bronchogenic carcinoma, experiments were carried out on normal dogs. Silver-coated Au^{198} (which has been shown to be more readily picked up by the pulmonary lymphatics than uncoated Au^{198}) was introduced into the lungs of dogs by two different methods.

The first method, endobronchial insufflation, was used in 8 animals which were subsequently sacrificed at varying time intervals. These animals showed no pleural effusions or gross mediastinal change, but the lungs exhibited hepatization of the treated lobe with areas of necrosis. The affected pulmonary areas later became fibrotic. Frequently, other lobes and occasionally the contralateral lung showed similar changes. Bronchi in the involved segments showed mucosal reaction and ulceration. With use of this method of administration, most of the radioactivity was retained in the lobe originally insufflated. Definite radioactivity was present in the lymph nodes, however. The lymphatic pick-up was delayed and irregular in distribution. There was no significant increase in the amount of lymph node damage beyond a dosage of 10–15 millicuries.

Following the observation of pulmonary damage secondary to the insufflation method, it was decided to use the submucosal injection method, and this was done in 15 animals, using varying dosages of silver-coated Au^{198} and sacrificing the animals at varying time intervals.

Use of this method eliminated the occurrence of

parenchymal pulmonary damage. In 2 instances, hydrothorax developed and in 3 instances edema and focal necrosis of the mediastinum occurred. There usually was considerable mediastinal and lymph channel reaction. All of these complications occurred during the second week following injection. Using this method, however, the Au^{198} concentrated in the lymph nodes rather than in the lungs. Lymph node pick-up occurred in three days. The lymph nodes showed progressively more widespread involvement and more damage with increase in size of dose and, in general, the lymph nodes closest to the site of injection showed the greatest damage, although this factor was variable. Changes in the lymph nodes varied in intensity and also in temporal sequence, not only in different lymph nodes, but also within the same lymph node. This suggests that succeeding waves of the colloidal Au^{198} are brought to the lymph nodes and that different parts of the lymph nodes pick up the colloid at different times. Au^{198} did not cause complete necrosis of the lymph nodes and regeneration occurred in eight weeks.

Examination of the liver, spleen, kidney and bone marrow showed minimal concentration of radioactive colloidal gold. The kidneys most frequently revealed microscopic changes in the tubular epithelium. Occasional areas of focal necrosis occurred in the bone marrow of the thoracic vertebrae.

The pattern of lymph node drainage was inconstant and in view of the intranodal variation which also occurred, the authors conclude that the most promising use of Au^{198} would be for small nodal metastases before they become grossly apparent.—*Robert W. Emerick, M.D.*

Boyesen, Svein, Campbell, James B. Stereotaxic implantation of calibrated Pd^{109} and Y^{90} spheres: a technique for producing predictable subcortical lesions in the brains of laboratory animals. *Yale J. Biol. & Med.*, Dec.–Feb., 1955/6, *28*, 216–224. (Address: S. Boyesen, Anatomisk Institutt, Oslo, Norway.)

Use of the Horsley-Clarke stereotaxic manipulator for ablation studies in the brain has been limited by want of a necrotizing agent that would gradually destroy a predictable volume of tissue. Radon has been used and found to produce a localized gradual destruction with little disturbance of adjacent and overlying structures. Drawbacks of radon were bulk and a certain percentage of gamma radiation.

Pure beta sources of less bulk were developed using palladium 109 and yttrium 90, artificially produced radioactive isotopes. These also allowed a reduction in size of the implant and provided a variation in half lives. These isotopes were formed into spheres with a diameter of 0.86 mm. and implanted with a stereotaxic manipulator. The lesions produced were best visualized by supravital staining and photographic recording. Their size was dependent on strength of source and degree of self-absorption within the source, half life of radioisotope used, and energy of beta emission. The lesion was at its maximum size on the fourth day and healing was evident at the fourth week. This would indicate that correlation of the area of destruction and physiologic changes cannot be made until at least the third postoperative week.

Changes produced by lesions in a few specific subcortical areas are discussed.—*Robert W. Emerick, M.D.*

van der Werff, J. Th. Bismuth-206, a pure gamma-emitter for therapy. *J. belge de radiol.*, 1956, *39*, 134–145. (From: Radiological Department, St. Canisius Ziekenhuis, Nijmegen, Netherlands.)

Bismuth 206, a cyclotron produced isotope, decays by K capture and a complex gamma spectrum with a mean energy of 0.75 mev.; the half-life is 6.4 days and the dose rate 1.9 r/hr./mc at 1 cm. The carrier-free Bi^{206}, as citrate, is mixed with a 5 per cent absorbent charcoal suspension in isotonic saline and then shows only very slight excretion.

This isotope has been used for local infiltration of tumors, where it is claimed that the absence of beta rays reduces the danger of local high dose concentrations and also intravenously for diseases of the reticuloendothelial system. The technique and apparatus for local injection is described, the dosage being based on the radium equivalent of 132 mg. hr. per cubic cm. and the result in one case is reported.

Intravenously, the bismuth-activated charcoal particles are taken up by the cells of the reticuloendothelial system, especially in liver, spleen and lymph nodes, but again the pure gamma radiation reduces local inhomogeneity of dose with less damage to healthy cells. The leukocyte count also shows a smaller reduction than with P^{32} or Au^{198}. There is loss of about 35 per cent by urinary excretion in the first twelve days.

The treatment of 2 cases of aleukemic lymphatic leukemia with good results after about two years is reported in some detail. Eight cases of Hodgkin's disease have also been treated during the past four years without recurrence. It is emphasised that radiobismuth, used by either method, provides a supplementary approach subsequent to orthodox roentgen or radium therapy.—*Raymond S. Quick, B.S.*

Looney, W. B. Late effects (twenty-five to forty years) of the early medical and industrial use of radioactive materials; their relation to the more accurate establishment of maximum permissible amounts of radioactive elements in the body. Part III. *J. Bone & Joint Surg.*, April, 1956, *38-A*, 392–406.

(From: United States Naval Hospital, National Naval Medical Center, Bethesda, Md.)

This, the third and last of a series of papers, completes an extensive study made in 1951, of 78 subjects who had received radium, mesothorium or radiothorium, either medically or while working as dial painters and should be read together with the earlier parts. (Ibid. December, 1955, p. 1169 and January, 1956, p. 175).

The methods for confirming the presence of radioactive materials in patients are listed and the clinical features briefly discussed. Hematologic changes are described and it is considered that there is little qualitative distinction between the effect of external on internal irradiation. There appears to be no correlation between the amount of radium retained and the onset of symptoms, but the incidence (14 per cent) of aseptic necrosis of the femoral head is unusually high, although this condition and also fracture of the femur only occur in the presence of 0.7–0.9 micrograms or more of retained radium; the average time of onset for all symptoms is fifteen years.

Tumor formation shows some relation to the route of absorption and the rate of ingestion of the radioactive material and, although the latent period before tumor development is in an inverse ratio to the amount of retained radium, the subsequent clinical progress appears to be independent of this factor.

The frequency and distribution of skeletal roentgenographic changes are tabulated; these occur only rarely with less than 0.5 micrograms, but with increasing frequency at 1.0 micrograms of radium and over. The increased accuracy of measurement of retained radium in these studies has only emphasized the complex nature of the relationship between this factor and the clinical picture and has mainly demonstrated that any increase in the permissible body burden for radioactive materials must be considered with caution.—*Raymond S. Quick, B.S.*

Kuhl, David E., Chamberlain, Richard H., Hale, John, and Gorson, Robert O. A high-contrast photographic recorder for scintillation counter scanning. *Radiology*, May, 1956, *66*, 730–739. (Address: D. E. Kuhl, Department of Radiology, Hospital of University of Pennsylvania, Philadelphia 4, Pa.)

A photographic detection device for scintillation scanning of patients who have received radioactive isotopes is described. The recorder produces high-contrast images on roentgen-ray film by means of a scanning light beam, the pulse frequency and pulse brightness of which increase with the count rate. Clinical trial has confirmed the usefulness of the device for the localization and recording of relatively small differences in radioactivity. A permanent record is produced on a transparent film base. This recorded image may be superimposed on a roentgenogram to permit accurate anatomic reference of the area under study.

Four principal advantages are claimed for this photographic recording method: contrast enhancement, variability of contrast, background suppression, and accurate anatomic localization.—*A. W. Sommer, M.D.*

Millar, Owen, and MacDonald, J. C. F. Radioactive gold in malignant effusions. *Canad. M. A. J.*, May 15, 1956, *74*, 783–788. (From: Department of Radiotherapy and Ontario Institute of Radiotherapy, Toronto General Hospital, Toronto, Ontario, Canada.)

The effects of the use of radioactive colloidal gold (Au^{198}) in 101 cases with malignant pleural and peritoneal effusions were studied at the Toronto General Hospital for a period of two and one-half years from 1952 to 1954.

The radioactive gold was rapidly injected through a No. 16 or 18 thoracentesis needle following aspiration of the effusion. A dose of 100 mc was injected into the pleural cavity and of 200 mc in the peritoneal cavity in the average case. Rubber gloves were employed and a collodion dressing was applied after the needle was removed. The patient changed position every five minutes for one hour. A rough scanning was done at that time and also 24 hours later. If a loculation was then found it was aspirated.

Mechanical complications such as difficulty in closing the puncture wound and equipment leaks occurred. A No. 16 or 18 thoracentesis needle solved the first problem. The radioactive gold was partially injected into pulmonary alveoli in one case when too much of the pleural fluid was aspirated. One patient developed a dermatitis as a result of being sensitive to the gold. Interstitial injection of the gold did not occur.

There were 116 instillations of the radioactive colloidal gold in 101 patients. The largest single group comprized patients with metastases from carcinoma of the breast; 44 chest instillations were done and 22 were improved; 6 abdominal instillations resulted in no improvement. The next largest group consisted of patients with effusions due to carcinoma of the ovary; there were 21 instillations in 18 patients; 4 cases with pleural effusion were improved out of a total of 7 and only 3 cases with ascites were improved out of 14 cases.

In 16 cases with secondary carcinoma from an unknown primary, there were 9 chest instillations with 4 improvements and 11 abdominal instillations with 6 improvements. The results in the lymphoma cases were disappointing.

The following conclusions were drawn: (1) the patients must not be cachetic and extremely ill; (2) radioactive gold should be used only if the effusions

develop rapidly after several aspirations; (3) it should not be used the second time if the first treatment was not successful; (4) it does not clearly prolong life; (5) it is impossible to predict which cases will respond; (6) the results in metastatic carcinoma of the ovary have been disappointing. In cases with abdominal masses, external radiation is best; and (7) there is a 40 per cent chance of relieving persistent fluid reaccumulation in malignant disease. The most favorable response has been in metastatic carcinoma of the breast with persistent pleural effusion.—*Charles W. Cooley, M.D.*

Lillie, A. B. Current techniques in the handling and distribution of cobalt 60 radiation sources. *Radiology*, June, 1956, *66*, 845–855. (Address: Atomic Energy of Canada Limited, Commercial Products Division, P. O. Box 93, Ottawa, Canada.)

The procedures and equipment involved in manufacturing and delivering cobalt 60 therapy sources are described.

In a reactor the outer layers of a neutron-absorbing mass will shield the inner layers from the neutrons. To reduce this self-shielding, the Canadian approach has been to use the cobalt in the form of small cylindrical pellets 1.0 mm. in diameter and 1.0 mm. long. These pellets can be held during neutron irradiation in thin cylindrical shells and then, after removal from the reactor, be transferred into a source container suitable for use in therapy machines.

Two approaches for handling high intensity radiation sources are described. First, for the so-called point sources, a small cell, well shielded by lead and fitted with a few interchangeable tools, has been employed. Here the operations are easily viewed and relatively delicate manipulations can be carried out. Second, for those sources which are large or distributed, a water-filled trench has been used. With this approach the operations are not as readily visible and precision operations cannot be carried out. However, the shielding is inexpensive and the shielded volume can be large.

For transferring or shipping sealed sources, the sliding drawer method is adaptable and easy to carry out. A two-drawer transfer case, a steel-enclosed lead container weighing about 1,800 kg. and having 25 cm. of lead for shielding, is used to ship new therapy sources. In replacing a source in a therapy unit the drawer plus the old source is drawn from the therapy unit into the transfer case and the new source and drawer are then moved from the transfer case into the therapy unit. An empty or dummy drawer is employed to follow up the full drawer during each transfer to avoid leaving an opening through which a dangerous radiation beam could emerge.—*Harold C. Hamilton, M.D.*

Backmann, R. Zur methodischen Problematik bei Stoffwechseluntersuchungen mit P^{32} nach Röntgenbestrahlung tierischer Tumoren. (The methodical problem in studies of metabolism with P^{32} after irradiation of animal tumours with roentgen rays.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, June, 1956, *84*, 713–719. (From: Institut für Medizinische Physik und Biophysik der Universität, Göttingen, Germany.)

The author makes an attempt to investigate the causes for the large variations in morphologic as well as metabolic changes which take place in transplanted mice or rat tumors after irradiation with roentgen rays.

The experiments were designed to study the effect of roentgen rays upon nucleic acid metabolism in the tumors, using P^{32} as an indicator. One hundred and twenty-three pure-bred B-1 mice with subcutaneously injected Crocker sarcoma 180 were used. The growth of the tumors was carefully recorded every two or three days. In a large majority of the animals the rate of growth observed was between 25 and 30 volume per cent per day but in a small percentage wide variations in the growth rate, between 5 and 60 volume per cent per day, occurred. The indicator P^{32}, was injected intraperitoneally in doses of 5 microcuries per gram body weight. For irradiation of the tumors with roentgen rays the animals were placed in a lead box with a suitable opening through which the tumor could be brought to the outside. Doses given were 3,000 roentgens (180 kilovolts, 10 milliamperes, ½ millimeter copper filter) and the dose rate in air at the site of the tumor was 290 roentgens per minute. Before irradiation the animals were injected subcutaneously with paraldehyde (0.01 milliliter of an 8 per cent solution per gram body weight) in order to keep them quiet.

It was observed that the rate of exchange of radioactive inorganic phosphate between serum and tumor tissue is influenced both by the rate of growth and by the total volume of the tumors. It is further influenced by irradiation of the tumors with roentgen rays and also by the injection of the paraldehyde. The possible sources of error in evaluating the results of such metabolic studies with P^{32}, notably after irradiation with roentgen rays, are discussed.—*Otto Glasser, Ph.D.*

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